Alternatives in the control of gastrointestinal endoparasitosis in sheep in the western amazon: literature review

Alternativas no controle das endoparasitoses gastrintestinais em ovinos na amazônia ocidental: revisão de literatura

Alternativas en el control de la endoparasitosis gastrointestinal en ovejas de la amazonía occidental: revisión de la literatura

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Alex Cicinato Paulino de Oliveira
Doutor em Ciência Animal
Instituição: Universidade Federal de Rondônia
Endereço: Rolim de Moura, Rondônia, Brasil
E-mail: alex.cicinato@unir.br

Sara Lucena de Amorim
Doutora em Medicina Veterinária
Instituição: Universidade Federal de Rondônia
Endereço: Rolim de Moura, Rondônia, Brasil
E-mail: sara.amorim@unir.br

Luciane Maria Laskoski
Doutora em Ciências Veterinárias
Instituição: Universidade Federal do Paraná - campus Curitiba
Endereço: Jardim das Américas, Curitiba, Brasil
E-mail: luci.laskoski@gmail.com

Ana Beatriz Nienke de Oliveira
Graduanda em Medicina Veterinária
Instituição: Universidade Federal de Rondônia
Endereço: Rolim de Moura, Rondônia, Brasil
E-mail: nienke37@gmail.com

Vinícius Costa Bandeira
Graduando em Medicina Veterinária
Instituição: Universidade Federal de Rondônia
Endereço: Rolim de Moura, Rondônia, Brasil
E-mail: viniciusbandeira746@gmail.com
ABSTRACT

Sheep farming is a business in permanent expansion in Brazil. Today, with 18 million sheep heads, the activity has grown virtually uninterrupted in the country, despite the difficulties. However, this livestock activity suffers great economic losses due to parasitism by gastrointestinal nematodes. Endoparasitosis is among the main causes of losses in sheep farming, causing a major obstacle to increasing production, leading to economic losses, including the death of animals. Thus, the proposal of this study is to review the scenario of sheep farming, as well as its difficulties, such as gastrointestinal endoparasitosis and its harmful effects on animal production. Faced with this problem, several control methods are addressed to reduce the effects caused by endoparasitosis, such as: use of anthelmintics and anthelmintic resistance, the Famacha method, integrated control and use of medicinal plants.

Keywords: Sheep farming, Helminthosis, Control, Resistance.
RESUMO
A ovinocultura é um negócio em permanente expansão no Brasil. Hoje, com 18 milhões de cabeças de ovinos, a atividade tem crescido praticamente ininterruptamente no país, apesar das dificuldades. Contudo, esta atividade pecuária sofre grandes perdas econômicas devido ao parasitismo por nemátodes gastrointestinais. A endoparasitose está entre as principais causas de perdas na ovinocultura, causando um grande obstáculo ao aumento da produção, levando a perdas econômicas, incluindo a morte de animais. Assim, a proposta deste estudo é revisar o cenário da ovinocultura, bem como suas dificuldades, como as endoparasitoses gastrointestinais e seus efeitos nocivos à produção animal. Diante dessa problemática, vários métodos de controle são abordados para reduzir os efeitos causados pelas endoparasitoses, tais como: uso de anti-helmínticos e resistência anti-helmíntica, método Famacha, controle integrado e uso de plantas medicinais.

Palavras-chave: Ovinocultura, Helmintose, Controle, Resistência.

RESUMEN
La cría de ovejas es un negocio en permanente expansión en Brasil. Hoy, con 18 millones de cabezas de ganado ovino, la actividad ha crecido prácticamente de forma ininterrumpida en el país, a pesar de las dificultades. Sin embargo, esta actividad ganadera sufre grandes pérdidas económicas debido al parasitismo por nematodos gastrointestinales. La endoparasitosis se encuentra entre las principales causas de pérdidas en la ganadería ovina, provocando un importante obstáculo al aumento de la producción, provocando pérdidas económicas, incluida la muerte de los animales. Así, la propuesta de este estudio es revisar el escenario de la ganadería ovina, así como sus dificultades, como la endoparasitosis gastrointestinal y sus efectos nocivos sobre la producción animal. Ante esta problemática se abordan varios métodos de control para disminuir los efectos causados por la endoparasitosis, tales como: uso de antihelmínticos y resistencia anti helmínticos, método Famacha, control integrado y uso de plantas medicinales.

Palabras clave: Ovinocultura, Helmintosis, Control, Resistência.

1 INTRODUCTION
Sheep farming in recent years has stood out in the productive scenario of the state of Acre, since it is a sustainable activity, with low-cost labor, in addition to having a fast financial return, generating stability, income and development in sheep production (Oliveira, 2018). The use of meat and its by-products represents one of the main sources...
of protein in human food, however, health problems have limited the productivity of these herds (Melo et al., 2013).

Helminthosis is the biggest health problem found in sheep farms. Infection by gastrointestinal nematodes is one of the main causes of losses in the production of small ruminants, since they cause great damage due to severe anemia, decreased production and reduced immunity, which may easily lead to death (Singh et al., 2014).

*Haemonchus contortus* is one of the most important parasitic species due to its high prevalence and pathogenicity (Corley & Jarmon, 2012). Treatment of these parasitic infections is generally based on strategic controls using anthelmintics. However, the resistance of the main nematode species to these chemical substances is a widespread phenomenon due to the presence of emerging strains with multiresistance, which can resist to all currently marketed anthelmintics (Singh et al., 2014).

2 LITERATURE REVIEW

2.1 SCENARIO OF SHEEP MEAT PRODUCTION IN BRAZIL

Brazil has a long tradition with sheep and goats, especially regarding the production of wool, milk and, more recently, meat. According to data from IBGE (2017), the country had a herd of sheep and goats of more than 18 and 9 million heads, respectively, showing a significant growth. Brazil is the main producer of sheep meat in South America, with 85,000 tons/year, which represents an increase of 20% compared with the volume produced in 2000 (Faostat, 2016).

Of the total number of sheep, 55.5% are located in the Northeast region and 24.4% in the state of Rio Grande do Sul, and the municipalities Santana do Livramento and Alegrete have the most numerous herds in the country. The rest of the Brazilian herd is located in the other states of the South region and in the North, Southeast and Central-West regions, as shown in Figure 1, discriminated by states (IBGE, 2016).
The current panorama of agrobusiness linked to sheep farming in the Western Amazon has also shown its economic difficulties in production and, especially, numerous health problems, among them constant parasitic infections, which is a concern to the expansion of sheep breeding in the region, precisely because it is the main health obstacle to increase the production of sheep meat (Guerra et al., 2012).

The progressive demand of consumption for sheep meat products have caused great changes in the production system, in order to improve the quality of the product more and more, mainly regarding the quality of the carcass (Grandis et al., 2016). In order for sheep farming to adapt to the conditions required by the consumer market, it is necessary to make new changes in the production, adjusting to the needs of the current industry, which seeks for young animals with greater weight gain and, consequently, improved carcass finish, with good muscle and fat coverage, while also seeking new methods of control regarding health (Silva et al., 2014). Consequently, the high increase in the prices paid to the producer makes this marketing activity an attractive medium for new enthusiasts of sheep farming, making it a great investment (Sorio, 2010).
Between 2010 and 2018, the state of Acre shows a significant development of this activity regarding the industry of sheep products. The installation of the refrigeration industry specialized in the slaughter of lambs, with specialized cuts, partnerships with the public sector, through the introduction of new animals of specific breeds for the production of meat with Santa Inês and Dorper breeds and the constant technical monitoring, has increased the scenario of the agrobusiness in Acre, due to the adhesion of small, medium and large breeders, turning the agrobusiness of sheep farming into a reality (Oliveira et al., 2016).

During 2017, the largest herds were located in the municipalities of Sena Madureira, Feijó and Rio Branco, respectively (Figure 2). As for distribution by mesoregions, the Baixo Acre region (formed by the municipalities Acrelândia, Bujari, Capixaba, Plácido de Castro, Porto Acre, Rio Branco and Senador Guiomard) concentrated 42% of the state herd, followed by the Alto Acre region (19%), Tarauacá/Envira (19%), Purus (17%) and Juruá (3%) (IDAF, 2017).

Figure 2. Estimated sheep herd in the state of Acre in November 2017. Distribution by municipality (Source: Adapted from IDAF, 2017).

Source: Authors
2.2 GASTROINTESTINAL PARASITES OF SHEEP

One of the factors of non-success in sheep farming, as reflected in the economic framework of productivity, is death due to failures in health management and the incidence of each disease, varying according to the herd breeding system. Endoparasitosis constitutes the main health problem with obstacles in sheep production throughout Brazil and worldwide, especially in tropical regions, where economic losses are more pronounced, with high mortality rates (Vieira, 2008).

In this aspect, gastrointestinal nematodes of the genera *Haemonchus* sp, *Trichostrongylus* sp, *Strongyloides* sp, *Cooperia* sp, *Bunostomum* sp, *Trichuris* sp, *Skrjabinema* sp and *Oesophagostomum* sp are the most prevalent (Vieira et al., 1998). Of these parasite genera, the most economically important are *Haemonchus* sp, *Trichostrongylus* sp, *Oesophagostomum* sp and *Strongyloides* sp (Brito et al., 1996), which will be addressed here with more detail due to the losses caused.

2.3 MORPHOLOGICAL CHARACTERISTICS AND BIOLOGICAL CYCLE OF SHEEP PARASITES OF GREATER ECONOMIC IMPORTANCE

The evolutionary cycle of trichostrongylid nematodes (family *Trichostrongylidae*), which includes *Haemonchus* sp., *Trichostrongylus* sp., *Oesophagostomum* sp. and *Strongyloides* sp., comprises a free-living phase in the environment and a parasitic phase in the host. The free-living phase starts with the elimination of eggs in the feces of contaminated animals into the environment. There, eggs become embryonic, the first stage L1 hatches, changes into L2 and evolves to the L3 infecting form, which has a double cuticle. The period from the elimination of the egg to the L3 larva varies from 5 to 10 days, depending on environmental conditions, mainly humidity and temperature. L3 migrates from the fecal bolus to the pasture, where it is ingested by animals along with forage, initiating the parasitic phase. The larvae reach the abomasus or the intestine, where they evolve to the fourth larvae stage (L4). Then, they...
reach the adult stage inside the parasitized organ, and, after copulation, the females begin oviposture. The pre-patent period varies from 14 to 28 days (Taylor, 2010).

*Haemonchus contortus* are medium, easy to observe. Males have a size of 10-20mm and females 18-30mm; at the height of the first third of the esophagus, there is a pair of strong papillae, directed back. The male has a dorsal lobe of the asymmetric bag and a short spike with a thin tip forming a hook. Females, most of the time, have a vulva covered by a well-developed vulvar labium (Ueno H. & Gutierres V.C., 1983).

*Trichostrongylus* sp are small sized, capillary, with length of less than 7mm and without buccal capsule, and short, twisted and usually pointed spikes. Several species of this helminth, in the adult form, are located in the small intestine of ruminants (Fortes, 2004).

*Oesophagostomum* sp has in its morphology two inflated structures that surround the body of the helminth worm, forming a cephalic hood (small structure that lies around the head) and cervical expansion (inflated cuticle with greater proportion).

*Strongyloides* spp. are intestinal helminths, comprising several animal species (Santos, 2009). Each species in the genus *Strongyloides* spp. shows an exclusive relation with certain hosts, with the main ones being *Strongyloides S. stercoralis* in humans and dogs; *Strongyloides papillosus* in ruminants; *Strongyloides S. ransomide* in pigs; *Strongyloides S. westeri* in horses and donkeys, *Strongyloides S. fuelleborni* in humans and African and Asian primates; *Strongyloides S. cebus* in American primates; and *Strongyloides S. rattie* and *Strongyloides S. venezuelensis* in rats (Monteiro, 2007; Bowman, 2010). The morphological characteristics of the first-stage larvae (L1) of *Strongyloides* sp. have a total length between 270 and 350μm, rhabditiform type esophagus, with distinct and evident body, isthmus and bulb with total length between 75 and 87.8μm. Males have a specialized structure that assists in copulation — the copulating bag, a ventral, prominent and elongated genital primordium, having between five and nine cells and a dorsal and a ventral cephalic lobe, separated by the buccal opening, which has an oval shape (Vieira, 2006; Bowman, 2010).
2.4 PATHOGENESIS, CLINICAL FINDINGS AND DIAGNOSIS OF THE MAIN PARASITES OF ECONOMIC INTEREST IN SHEEP

*Haemonchus. contortus* has a high degree of hematophagism, and increases blood loss of the host due to the inoculation of anticoagulant substances in the place where they are fixed (Hastenpflug & Womme, 2009). In the pathogenesis of *H. contortus*, lesions in the gastric epithelium cause a reduction in the secretion of hydrochloric acid (HCl) and pepsinogen, resulting in an increased pH, inactivating pepsin and, consequently, interrupted protein digestion (dyspepsia). A classical sign of reduced plasma proteins (especially albumin) is submandibular edema (Costa & Borges, 2010).

Thus, the most obvious clinical signs of infection with *H. contortus* are pale mucous membranes, bristly and dull fur, severe anemia, ascites and lethargy, characterized by a progressive drop in hematocrits in a short period of time. Hypoproteinemia and hypoalbuminemia are also observed (Soulsby, 1987), due to the high level of parasitic infection, in which the animal may lose up to 145mL of blood per day. Consequently, it may develop a submandibular edema, ascites and slimming by protein loss, in addition to digestive disorders, such as diarrhea (Fortes, 2004).

Regularly asymptomatic, in large proportions, infections caused by this parasite develop the ability to produce lengthy and strenuous watery diarrhea, especially in poorly fed goats (Georgi, 1998). At lower levels of infection, inappetence and growth reduction, sometimes accompanied by soft stools, constitute the most common symptomatology (Urquhart et al., 1998).

In tricostrongylose, parasites of the genus *Trichostrongylus* sp. are located between the glands of the intestinal mucosa, causing inflammatory reactions, with superficial erosion, hyperemia, edema, and overflow of plasma into the intestinal lumen, with loss of proteins. Villi decrease, limiting the area of absorption and causing diarrhea (Echevarria, 1996).

*Oesophagostomum* sp. causes the development of nodules in the intestinal mucosa, due to a chronic inflammatory process caused by the migration of larvae. The emergence of larvae from the intestinal wall to the lumen causes catarrhal colitis, increased number
of mucus-producing cells and loss of albumin to the lumen of the organ, determining the appearance of diarrhea (Riet-Correa et al., 2001). These nodules are hardened on the wall of the organ (mainly visible in the serosa), with mean diameter of 0.5 mm and whitish coloration, as observed by Taylor et al. (2010), who stated that nodules are visible to the naked eye, with a diameter varying from 0.5 to 3 mm.

These authors also reported that similar nodules may be found in the liver, lungs and mesentery, and that, in most cases, such nodules are necropsy findings. The mucosa and intestinal content do not show alterations, as well as the other organs, being, therefore, necropsy findings and reports in literature.

In acute infections by *Oesophagostomum O. columbianum*, according to Taylor et al. (2010), there is diarrhea, weight loss, emaciation and prostration, while in chronic infections, there is inappetence and emaciation with intermittent diarrhea and anemia. However, it is not possible to observe clinical signs or any other changes related to the presence of the parasite, unlike animals with haemoncosis, where the parasite, because it is hematophagous, may be responsible for the main changes in the animal and even for its death.

Currently, strongyloidosis is considered one of the most important gastrointestinal nematode disorders of production ruminants (Andrade, 2010). In Brazil, the situation is favorable to the occurrence of this parasitosis, due to climatic conditions that allow a good level of egg development and hatching of the larvae that will infest pastures (Braga et al., 2001; Andrade, 2010).

Strongyloidosis affects calves and lambs. *Strongyloides* sp. are located on the epithelium of the mucosa of the small intestine, causing inflammatory reactions with edema, erosion of the mucosa, and catarrhal enteritis. Since infection occurs through the active penetration of infectious larvae through the skin, dermatitis might be found on the paws, which affects the movement of the animal. Due to the biological cycle of these parasites, consequently, the larvae migrate to the pulmonary parenchyma, causing respiratory disorders (Radostitis & Blood, 1994). Once in the organism of ruminants, the infecting larvae of *Strongyloides S. papillosus* starts its parasitic cycle and, as it penetrates
into the tissues of the animal, it causes a series of clinical signs, which can lead to sudden death, characteristic of strongyloidosis (Anderson, 2000; Andrade, 2010).

In general, the main clinical findings of parasitic infections are severe anemia, weight and appetite loss, diarrhea with watery or hemorrhagic feces, prostration, weakness and tremor in the early stages of the inflammatory process. In the chronic phase, there is submandibular edema, debility and reduced production (Cavalcanti et al., 2007).

The main form of laboratory diagnosis comprises parasitological examination, which is represented by fresh stool samples and analyzed by the total of eggs per gram of feces. The main parasitological techniques employed are: EPG (Gordon & Whitlock, 1939, modified) and coproculture (Robert O'Sullivan, 1950) tests. In cases of hermoncosis, the percentage of hematocrits should be evaluated, since *Haemonchus* sp. shows hematophagism, thus triggering a case of anemia and hypoproteinemia. Hypoproteinemia leads to a drop in capillary colloid osmotic pressure, generating retention of the interstitial liquid, which is characterized by edema.

2.5 CONTROL MEASURES ON GASTROINTESTINAL NEMATODES OF SMALL RUMINANTS

Due to the problems arising from endoparasitosis, several control measures must be applied in an attempt to reduce parasitic load and/or minimize the deleterious effects on the host. The following describes the most commonly performed forms of control:

2.5.1 Use of Commercial Anthelmintics

As documented, the first anthelmintics used came from natural drugs. At first, copper sulfate was used in 1881, and tetrachloride in 1926. In the 1940s, phenothiazine and piperazine were inserted for the treatment of gastrointestinal nematodes. In 1960, anthelmintics with a broad spectrum of activity, greater efficacy and lower toxicity were widespread. From this moment, broad-spectrum anthelmintics of three pharmacological
groups, with multiple action mechanisms, have been applied for years, which are benzimidazoles, imidazothiazoles and macrocyclic lactones (Martin, 1997).

Currently, a new drug with a differentiated action mechanism has been developed, monepantel, the first representative of the group of amino acetonitrile derivates (Kaminsky et al., 2008a). This group of drugs acts as an agonist of ion channels, which causes hyperdespolarization with contraction and consequent spastic paralysis of the nematode (Spinosa et al., 2014).

Levamisole belongs to the class of imidazothiazoles. The activity of imidazothiazoles leads to starvation of the helminth and consequently to its death, since they act as nicotinic muscle receptors, causing spasmodic paralysis in nematodes (Sangster et al., 2005). This class of antiparasitic drugs acts as cholinergic agonist on the membrane of the musculature cells of nematodes. It is believed that factors linked to resistance to levamisole involve the loss of sensibility against these anthelmintics in the subunit of the cholinergic receptor of the parasite (Molento, 2004).

Albendazole (benzimidazole) acts on microtubules, a fundamental structure for cell maintenance, such as cell absorption and secretion, the anchoring of membrane receptors in specific sites, for example, in nerve synapses, mitosis and meiosis, among other functions (Caviston & Holzbaur, 2006). Benzimidazoles cause the shortening and disappearance of the microtubule, hindering the essential functions of the cell (Prichard, 2008), which leads to cell death.

Macrocyclic lactones form a group of drugs, represented by avermectin and milbemycin. Macrocyclic lactones act on neuroneural and neuromuscular synapses, increasing the inhibitory postsynaptic potential (IPSP), which causes paralysis and death of nematodes by decreased neurotransmission (Sangster, et al., 2005). The selective paralysis of parasites is related to the increase in permeability of chlorine ions (Cl-) in the muscle, potentializing the ion channels mediated by glutamate (GluCl) (Martins, 2016).

In the chemical group salicylanilide, closantel (n-5-chloro-4[4-chlorophenol]-2-metholphenol-2hydroxy-3,5-diiodobenzamine) stands out. This active principle is mainly used against Oestrus ovis, Haemonchus sp., Fasciola hepatica and other hematophagous nematodes of cows, sheep and goats. Its mechanism of action consists in binding plasma
proteins (albumin) in the blood, and, when the blood is ingested by the parasite, closantel, which is linked to plasma proteins, acts by interfering in the ATP synthase through the mitochondria of the cells of the parasite, uncoupling their oxidative phosphorylation (Michiels, 1987).

In general, regardless of the mechanism of action of anthelmintics, these interfere in the cellular metabolism, causing the death of the parasite, either by starvation or paralysis (Molento, 2004).

Anthelmintics may exert their actions through opposite mechanisms of actions, but, in general, they are grouped into two categories: those that act more quickly in cell membrane ion channels, and those that act more gradually in biochemical cell processes (Lecová et al., 2014). In this way, they may impair the production of energy, the neuromuscular conformation and microtubular efficiency, leading to elimination of the parasites due to weakness or expulsion by paralysis (Spinosa et al., 2014; Górniak; Bernardi, 2014).

In Brazil, the strategic controls with deworming, used as a method to combat helminthoses, aiming at reducing the number of infectious forms in pasture, is still the most used form, although it favors the spread of resistant populations due to numerous factors. However, the objective of strategic dosages is to administrate anthelmintics when parasites are in fewer numbers in the pasture, or in times when the climatic conditions are unfavorable to the survival of the free-living stages (Riet-Correa, 2001).

The use of strategic deworming schemes in the treatment of helminthoses, recommended as being more efficient, is the application of the 1st deworming in the first month of the dry season of the year; 2nd deworming 60 days after the 1st, 3rd deworming in the second to last dry month, and 4th deworming in the middle of the rainy season (Rosa et al., 1986).

Additional anthelmintic protocols, called tactics, are carried out in certain circumstances, such as in herds that use breeding season, in which a therapeutic medication is applied before the beginning of the copulation or artificial insemination, and another 30 days after the beginning of the birth period (Vieira et al., 1997). In other ecosystems in the country, the dosage times are adapted according to the local climatic conditions.
conditions, always seeking to concentrate the anthelmintic treatment in the dry period. In the state of Minas Gerais, producers deworm their animals every four months, with average interval of 3.6 months (Guimarães et al., 2009).

Duarte et al. (2012) found a reduction in the EPG count of animals treated in relation to the control group for all evaluated properties in northern Minas Gerais. The percentage of efficacy ranged from 90 to 100% for animals treated with levamisole, and from 56.3 to 100% for lambs dewormed with albendazole. Levamisole was more effective (p<0.05) in reducing the mean EPG of the nine evaluated herds.

Lopes et al., (2013) made two experiments, in which 15 sheep in the rearing period were used, being 8 mixed-breed females and 7 mixed-breed males, in the region of Taiano, Roraima. In Experiment 1, after 14 days of treatment, they observed an anthelmintic efficacy of 12.58% in treatment with albendazole, and 7.13% in the treatment with ivermectin. They considered that the gastrointestinal helminths in the herd were resistant to the two active ingredients used. Experiment 2 was performed with closantel, levamisole and moxidectin, and obtained a 100% efficacy.

Although monepantel is the only active ingredient that is still described for having excellent efficacy against the genus *Haemonchus*, sp. a study by Cintra el al. (2016) showed low efficiency after its application in sheep herds in a region of the state of Acre, corroborating with recent results described in the state of São Paulo, Brazil (Martins, 2016), New Zealand (Scott et al., 2013), Uruguay (Medeiros et al.,2014; Ramos; Banchero, 2014) and in the Netherlands (Van Den Brom et al., 2015).

The best strategy to carry out preventive treatments with commercial anthelmintics is through the application in continuous periods on predetermined dates, involving the whole herd, in order to avoid clinical or subclinical infections. However, there is no 100% elimination of infectious forms, selecting resistant strains (Molento, 2008). It is recommended that curative treatment should be performed when obvious clinical signs or even death from parasitism occur. Tactical treatment should be used whenever environmental conditions favor the emergence of helminthoses. Both in curative and tactical treatment, the development of resistance is delayed, but there is an important loss of production by animals, in addition of high contaminations of the
environment with the infecting stages of nematodes. Suppressive treatment consists in
deworming animals every 2-4 weeks, with short persistence drugs.

The reason for this is to employ drugs before the end of the pre-patent period of
the parasites, thus aiming at a near total elimination of helminth worms in the environment
(Torres-Acosta & Hoste, 2008). However, although it is efficient in controlling
parasitism, it precipitates the rapid appearance of anthelmintic resistance. Selective
treatment is when only some animals of the herd are treated. And, finally, unintentional
treatment is when anthelmintics are used to treat other parasitic diseases, such as myiasis
by *Oestrus ovis*, or mange (Torres-Acosta & Hoste, 2008).

2.5.2 Resistance from the Use of Commercial Anthelmintics

The control of helminthoses based only on the administration of anthelmintics
often does not have good results, especially due to the development of parasitic resistance
to these medications (Vieira, 2008). For this reason, the most observed resistance
mechanisms for the main anthelmintics are described below.

Anthelmintic Resistance (A.R.) is an episode in which some organisms of the
population are able to resist after continuous use of a chemical compound (Molento,
2004). Anthelmintic resistance is defined as a considerable evolution of the number of
species, in a certain population, prepared to withstand doses of a chemical compound that
was lethal for most representatives of a population, usually vulnerable and of the same
species (Vieira, 2008).

Cavalcante et al. (2009) defined parasitic resistance as the phenomenon that
prevents a drug from maintaining the same efficacy against parasites, if used in the same
conditions and after a certain period of time. Coles et al. (1992) suggested that it occurs
when the efficacy of the normal therapeutic dosage is below 95%.

The resistance mechanism may be related to the non-recognition of membrane
receptors by the drug used, a change in the physiological metabolism of the animal that
inactivates or removes the drug, alteration in pharmacokinetics, compromising the
distribution of the drug to its sites of action, or amplification of the target genes to
overcome drug actions (Wolstenholme et al., 2004). The ability of some endoparasites of surviving future expositions to a drug may be spread to their successors.

Genes for resistance are rare (around 5%) within a population. However, as the selective agent is used frequently, the proportion increases and failure in control may quickly appear. Usually, resistance is suspected when a low response is obtained after an anthelmintic treatment (Torres-Acosta; Hoste, 2008). On the other hand, a lack of response to the vermifuge does not necessarily mean a case of resistance, since some clinical signs, generally associated with gastrointestinal parasitism such as diarrhea, enema and loss of body condition, are non-specific and may be due to other factors, e.g. the presence of infectious agents, poor nutrition, deficiency of mineral elements and poisoning by plants (Torres-Acosta; Hoste, 2008).

Researches show that the resistance to benzimidazoles is related to the mutation of the amino acids phenylalanine and tyrosine (Kwa et al., 1994). This change reduces the binding affinity of the drug with the recombinant protein (Lubega & Prichard, 1991).

Macrocyclic lactones form a group of drugs, represented by avermectin and milbemycin. The loss of receptors or the decreased local affinity for the drug are the main mechanisms used by helminths to acquire resistance to these drugs (Köhler, 1991).

The occurrence of anthelmintic resistance is described by some authors worldwide, including in Brazil, gradually disseminating through all states with significant sheep farming (Sczesny-Moraes et al., 2010). Thus, several studies prove the anthelmintic resistance to different chemical groups, as described in Table 1.
Table 1. Initial histories of anthelmintic resistance in Brazil and other countries.

<table>
<thead>
<tr>
<th>Regions/Countries</th>
<th>Chemical groups</th>
<th>Author/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>South</td>
<td>Ivermectina, Levamisole, Closantel, Albendazole</td>
<td>Vila Nova et al., 2014.</td>
</tr>
<tr>
<td></td>
<td>Albendazole</td>
<td>Ramos et al., 2002.</td>
</tr>
<tr>
<td>Northeast</td>
<td>Ivermectina, Levamisole, Closantel, Albendazole</td>
<td>Rosalinski-morais et al., 2007.</td>
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<td></td>
<td>Closantel, Albendazole</td>
<td>Lopes et al., 2014.</td>
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<tr>
<td>Argentina</td>
<td>Levamisole</td>
<td>Melo et al., 2013.</td>
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<td>Albendazole</td>
<td>Lima et al., 2010.</td>
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<tr>
<td>Malásia</td>
<td>Levamisole, Closantel</td>
<td>Fiel et al., 2011.</td>
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<td>Colômbia</td>
<td>Ivermectina, Levamisole</td>
<td>Leathwick et al., 2012.</td>
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<td>Albendazole</td>
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<td></td>
<td>Closantel</td>
<td>Waghorn et al., 2014.</td>
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With reports beginning in the South region, resistance was detected in 28 cities in Paraná (Cunha & Filho, 1999), Santa Catarina (Ramos et al., 2004) and again in Rio Grande do Sul (Echevarria & Trindade, 1989; Echevarria et al., 1996). Since then, there have been several reports of cases of resistance throughout the country in the Northeast (Vieira et al. 1989, Melo et al., 2013), Southeast (Veríssimo et al., 2002) and Central-West (Sczesny-Morais et al., 2010) regions.

Soon after the first report of resistance to anthelmintics in sheep in Rio Grande do Sul (Dos Santos; Gonçalves, 1967), there was no shortage of reports of isolated drug resistance. Echevarria, Pinheiro and Corrêa (1989), when examining herds in the municipality of Bagé-RS, found herds with helminths resistant to benzimidazoles, tetramisole, and herds with multiple resistance. A study conducted in Rio Grande do Sul by Cezar et al. (2010) showed that, in anthelmintic efficacy tests, there was no reduction
in EPG count, thus concluding the presence of resistance to levamisole, moxidectin, albendazole, ivermectin, nitroxil, disophenol, trichlorfon, closantel and a combination of ivermectin + levamisole + albendazole.

The helminth egg count reduction test per gram of feces was used to test the efficiency of anthelmintics in 42 sheep farming properties in five different regions in the state of Paraná, Brazil. Five drugs were used individually or in combinations (benzimidazole, imidazothiazole, ivermectin, milbemycin and closantel). Results showed that the prevalence of resistance was high for all anthelmintics evaluated: 88.1% for benzimidazole (oxfendazole), 78.6% for ivermectin, 56.4% for closantel, 38.7% for closantel + oxfendazole, 38% for levamisole, and 23.6% for moxidectin. There was multiple resistance in all farms studied (Thomaz-Soccol et al., 2004).

Other factors may also contribute to an apparent failure of anthelmintic treatment, without the parasites becoming resistant. Some of these factors include: fast reinfection due to highly contaminated pastures; presence of inhibited (hypobiotic) or fully developing larvae that are not affected by the anthelmintic; defects in the dosing gun, thus resulting in the administration of an underdosage, and the wrong choice of vermifuge for the parasite to be controlled (Baker, 1975). In any investigation on the possible failure of an anthelmintic, it is necessary to obtain information on the type of parasitic control that is used in the property and on the drugs used at the time or in the past (at least the last five years), dosages and frequency of anthelmintic medications, management history, purchase and loan of animals, age of the animals and previous seasonal conditions and at the time of treatment (Vieira, 2008).

The development of isolated parasites resistant to various classes of anthelmintics is a common phenomenon in many countries, identified in many species of nematodes (Kaplan, 2004), reaching levels that impair the breeding of sheep in some regions of the South hemisphere (Jackson; Coop, 2000). Faced with the problem of anthelmintic resistance, other control methods should be present to minimize its effects on parasitism.
2.5.3 Use of Integrated Controls

The control of parasitosis is of fundamental importance for livestock (Heinzen et al., 2012). Usually, associations of several prophylactic measures are used, and the strategies might vary from a simple reduction in the prevalence of the disease, aiming at obtaining a satisfactory health level, that is, total destruction of the pathogen agent in the contaminated environment (Ramos, 2013). An effective planning of control and prophylaxis should be based on data on the epidemiology and life cycle of the helminths predominant in the region, the impact of the disease and valorization of costs and privileges that come from their fight (Pereira, 2011).

The problem caused by gastrointestinal nematodes may be minimized by rearing breeds that are more resistant to infections (Amarante et al., 2004). This measure associated with management techniques that aim to reduce the contamination of pasture with nematode infecting larvae may represent an important advance in the control of the worms, greatly reducing the dependence of antiparasitic agents to the prophylaxis of helminthoses. The consortium of animals of different species may reduce the number of specific parasites of sheep and goats, and it may be mixed or alternated at different moments (Souza et al., 2005). In mixed grazing, good results are obtained when susceptible animals share the pasture with resistant animals of the same or another species. The efficiency of this method depends, among others factors, on the specificity of parasites. Larvae of parasites with high parasitic specificity are destroyed when ingested by an animal of another species (Barger, 1997).

The influence of the nematode genus has variations that oscillate, according to geographical region, climate, consortium with other animal species, type of management, among other regional factors (Amarante et al., 1992).

In relation to animals, age, nutritional state, delivery, lactation, breed, parasite, management, birth, weaning, overpopulation and the introduction of new animals into the herd are factors that contribute to increase the parasite population in the organism of the animals (Quadros & Vielmo, 2004).
Dividing animals into categories is important not only for the correct management of pastures, but for all herd activities. By separating animals by age and physiological state, it is possible to better meet the nutritional requirements of each phase, take better care of more sensitive categories and to plan control strategies specific for these animals (Quadros, 2004).

According to Pereira et al. (2005), an alteration in life cycle occurs when environmental conditions are unfavorable, such as cold weather, desiccation or even the resistance of the host, leading the ingested larvae to remain inhibited in the mucosa of the digestive tract, thus prolonging the pre-parent period. The end of the inhibition may be caused by the arrival of Spring, decreased resistance, approaching delivery, introduction of animals in parasite-free areas, or even by anthelmintic treatment (drugs that do not affect inhibited larvae).

Also, it is known that these larvae are quite resistant, and may remain for several months in pastures. In the hottest and sunniest hours, they head to the lower parts of the plants, even penetrating the surface of the soil in search of a more conducive environment to their survival (Belluzo et al., 2001).

Pasture rotation, therefore, as a method of parasitic control, aims to reduce the levels of contamination of pastures and the risks of animal infection. The process consists in absenting animals from a certain part of the pasture, for a sufficient period to prevent the evolution of the life cycle of the parasite. Having no way to complete the parasitic phase in the animals, larvae end up dying (Láu et al., 2002). In this way, pasture rotation is a very common practice, especially from an agrostological and zootechnical point of view (Amarante, 2005), being frequently mentioned as a way to decrease populations of larvae in pastures (Bueno, 1998; Nunez, 1999).

This method, however, shows much more favorable results in regions of humid tropical climate, where infecting larvae, in pasture, have a shorter survival period (Banks et al., 1990). In the region of Botucatu-SP, the pastures used in the rotation scheme remained at rest for periods that varied from 30 to 40 days, which, in most situations, were too short to reduce the parasitic load in the pasture (Amarante, 2005).
In the region of Lages-SC, the period of decontamination of native pastures necessary for an appreciable reduction of the number of L3 varied throughout the year. It took from 42 to 56 days in Spring, 70 to 84 days in Summer, 112 to 126 days in Autumn and 98 to 112 days in Winter (Souza et al., 2000). Thus, surveillance in relation to helminthosis should be redoubled when these grazing systems are adopted, especially in regions with a more temperate climate.

2.5.4 Famacha Method

The strategic scheme recommended for the control of helminthosis in small ruminants aims at reducing the amount of helminths when they are found in fewer numbers in pasture, that is, during the dry season. This short-term planning has allowed excellent results, however, when used throughout the year, without implantation of other alternatives, it may cause resistance in the population of parasites (Molento, 2004).

In this context, the Farmacha method was developed in South Africa by Van Wyk et al. (1997), which aims to clinically identify animals that show different degrees of anemia, caused mainly by infection by *H. contortus*, which allows a selective treatment, without the need to resort to laboratory tests (Molento et al., 2004). According to Van Wyk et al. (1997), there is a significant correlation between the colorations of apparent mucosa and globular volume, allowing to identify animals capable of surviving an infection by *H. contortus*.

Thus, the Farmacha method suggests medicating the lowest possible number of animals with less parasitism, that is, only animals that show signs of clinical anemia should receive anthelmintic treatment. This method suggests that there will be persistence of a sensitive population in the environment, maintaining anthelmintic efficacy for a longer period and, with this, the appearance of parasitic resistance tends to be delayed.

In addition, the Farmacha method allows an average saving of 58.4% in costs with the purchase of anthelmintics (Bath & Van Wyk, 2001) and reduces contamination by chemical residues in milk, meat and the environment, which is a matter of global concern (Herd, 1995; Van Wyk et al., 1997). Another advantage of the method is to allow the
selection of animals genetically resistant to helminthosis, as well as being simple, cheap and easy to be implemented, including for people with a low level of education (Vatta et al., 2001).

2.5.5 Herbal Medicines in Veterinary Medicine

The demand for new antiparasitic compounds of plant origin is due, first of all, to the shortage of commercial anthelmintic compounds that eliminate parasites. There are only nine chemical groups of medicines available, and a large part of nematodes are already resistant to most of them (Veríssimo et al., 2010).

Worldwide, there is an increase in the number of researches involving herbal medicines that indicate activity against virus, bacteria, fungi and parasites. The same happens in the field of veterinary medicine, in which research with medicinal plants is aimed at controlling several diseases that compromise animal productivity (Niezen et al., 1996).

In different ecosystems, a range of phytochemical compositions may be found with a lack of specific research. In the midst of several existing plant species, some may have anthelmintic activity. Another motivation for the interest in researching medicinal plants in nature in order to control parasites is the concern to use antiparasitic compounds that restrict the contamination disorder of the environment and that do not accumulate toxic residues in meat and/or milk destined for human consumption (Chagas, 2004).

The application of medicinal plants in the treatment or prevention of routine diseases in animal farming is an activity that passes on for several generations, and continues to be used by people mainly from rural areas. Many reasons have contributed to the growth in the use of this resource, such as the high cost of industrialized medications, difficult access of the population to medical assistance, as well as the tendency to use natural products (Bernardes et al., 2011).

Several plants are known to have anthelmintic activity; however, their efficiency must be proven through scientific research. Studies involving herbal products for disease
control are still scarce (Vieira et al., 1999). Several plants and natural compounds with anthelmintic effects are described below.

According to Githiori et al. (2006), given the cultural understanding, several medicinal plants are recommended to control parasitic diseases, such as the seeds or leaves of plants as Allium sativum (garlic), Allium cepa (onion), Mentha (mint), Walnut, Pimpinella anisum (anis) or parsley, which have been used to protect animals with parasitism by gastrointestinal nematodes, while cucumber and pumpkin seeds have been associated with the expulsion of cestoids from the gastrointestinal tract.

In the state of Piauí, 14 plants with anthelmintic activity were listed by Girão et al. (1998), based on information from goat farmers. The related plants were Cucurbita moschata (pumpkin), Luffia operculata (sponge cucumber), Operculina sp. (Batata-de-purga), Heliotropium sp. (Crista de galo), Mentha sp. (Mint), Carica papaya (papaya), Chenopodium ambrosioides (Mexican-tea), Momordica charantia (bitter melon), Milome (unidentified scientific name), Plumeria sp. (Pau de leite, Janguba), Jatropha curcas (purging nut), Scopalaria dulcis (sweet-broom) and Croton sp. (rushfoil).

Vieira et al. (1999) assessed the anthelmintic efficacy of nine plants on H. contortus in goats. Anona squamosa and Momordica charantia reduced the number of adult helminthosis, respectively, by 30.4 and 17.6%.

Batista et al. (1999) observed that Momordica charantia and Spigelia anthelmia inhibited egg development and immobilized larvae of H. contortus. These results were subsequently confirmed by Assis (2000), who showed the ovicide and larvicide activities of ethyl acetate and matanolic extracts in gastrointestinal nematodes of goats. Pessoa (2001) observed in vitro ovicide activity in the essential oils from Chenopodium ambrosioides, Ocimum gratissumum, Lippia sidoides, Croton zehntneri and Aazadiractina, active ingredient of Azadirachta indica (neem tree), on H. contortus.

In the state of Acre, Amorim (2019), when assessing the ethnoveterinary study in a rural community, observed that the plants with greater indication in animal treatment were those which act on the gastrointestinal system, such as (mint) – Mentha spicata, (bitter melon) – Momordica charantia, (crajirú) – Arrabidaea chica (papaya) - Carica papaya (Mexican-tea) – Chenopodium ambrosioides, (purging nut) – Jatropha curcas,
(melissa)- *Melissa officinalis* (9/0.15), and (lemon grass) - *Cymbopogon citratus* (9/0.15). These plant species with higher use value have a proven scientific knowledge, such as its phytochemical composition and pharmacological activities.

Fruits, leaves and roots of *Mormodica charantia* (Cucurbitaceae) are used to treat ailments, being used for wound healing, endoparasitosis, ectoparasites and in the treatment of colic (Cordeiro et al., 2010). Phytochemical studies have shown biologically active compounds such as glucosides cucurbitins and cucurbitane (Chenj et al., 2008).

Other studied plants with anthelmintic action are described below. *Jatropha curcas* (Euphorbiaceae) have secondary metabolic compounds such as tannins, catechins and triterpenes, showing anthelmintic action (Monteiro et al., 2011).

*Melissa officinalis* (Lamiaceae), popularly known as lemon balm, has been mentioned with antibacterial and antioxidant properties, used in the treatment of gastrointestinal diseases (Nascimento et al., 2000), with calming effect (Kennedy et al., 2004). The plant has a component with a potent inhibitor of Gamma-aminobutyric acid transaminase (GABA), which explains its anxiolytic effect; rosmarinic acid has been identified as the main bioactive substance, acting as a repellent and in mental performance by working on muscarinic and nicotinic acetylcholine receptors (Kennedy et al., 2003). It has eugenol, tannins and terpenes as main secondary metabolic compounds.

*Carica papaya* (Caricaceae), popularly known as papaya, have anthelmintic properties, providing 97% of efficacy against infection by *Tricuris suis* in pigs (Levecke et al., 2014). They also have a potent in vivo effect in abomasus nematodes, such as *H. contortus* of small ruminants (Buttle et al., 2013). Other plant species, also from the Meliaceae family, have been reported with anthelmintic potential. Cala et al. (2012), when assessing plant extracts of *Melia azedarach* and *Trichillia claussenii in vitro* on gastrointestinal nematodes of sheep, observed greater anthelmintic activity on the larval development and low efficiency as ovicide. Brito et al. (2009) observed in vitro anthelmintic activity of the aqueous and ethanol extract of *Morina citrifolia* in chicken.
nematodes (*Ascaridia galli*) with product efficacy of 50% and 77%, respectively. Tests *in vivo* of the *Canthium mannii* in rodents infected by *Heligmosomoides polygyrus* showed that this compound is effective both in the reduction of the egg count in the feces and in the reduction of total worm count, with 75% and 84% efficacy, respectively (Wabo Pone et al., 2009).

Amorim (2021) observed anthelmintic efficiency in the ethanol extract of the andiroba *Carapa guianensis* (Meliaceae) stem on sheep nematodes, observing an 86% and 70% reduction in the parasitic load, respectively.

It is possible that the results found in the different plants mentioned here are linked to condensed tannins, since this chemical compound has the ability of binding chemical complexes of the parasite, by affecting the biology of nematodes, interfering in mortality, the process of cuticular elimination, egg hatching and larval development (Fernex et al., 2012). Therefore, they affect the reproductive function of nematodes, reducing the number of eggs in sheep farming, considerably decreasing the number of infecting larvae in the environment or improving the immune response of the animals against parasites (Macedo et al., 2012).

Many plants are particularly known to have anthelmintic activity. However, the total scientific acceptance of drugs derived from phytotherapeutic plants in veterinary medicine will only happen if these products perform in the same parameters of efficacy, safety and quality control as synthetic products (Rates, 2001).

The initial tests to observe the anthelmintic efficacy of a medicinal plants are performed *in vitro*, due to the simplicity of execution, low cost and celerity compared to tests *in vivo*. Plants, or their compositions, are arranged directly in proximity with several stages of development of the parasite, seeking to evaluate its impact on egg hatching, larval evolution and mobility of larvae and adults. It is essential that these first tests have a specific targeting against the helminths of greater economic importance (Hammond; Fielding; Bishop et al., 1997). Among the *in vitro* tests, those that can be used to evaluate the anthelmintic effects of a plant are: egg hatching inhibition test (EHI), larval migration inhibition test (LMI), larval feeding inhibition test (LFI), ensheathment test (ET), larval development test (LDT) and adult motility test (AMT) (Jackson; Hoste, 2010). According
to the authors, for the first analysis of a plant, EHI, LMI and LFI tests may be performed, due to their practicality.

It is essential to describe the many aspects involved, such as the part, age and physiological state of the plant, terrain in which it is found, particularities related to extraction and compatible dose. Conditions related to the animal (species, age, physiological state) should as well be weighted so that it may be used in the control of nematodes. It is interesting to note that the beneficial and harmful effects caused by the possible compositions depend on many factors, especially the concentration, structure of these compounds and frequency of ingestion and administration (Hoste et al., 2006).

3 FINAL CONSIDERATIONS

Gastrointestinal endoparasitosis causes economic losses, which is important for sheep farming. For its efficient control, it is necessary to change the current schemes of preventive treatments, which currently favor the development of resistance, replacing them with other control systems that decrease parasitic load. Thus, the use of anthelmintics must be administered with caution, using them in correct amounts and associating them with other alternative treatment methods that are capable of decreasing the number of strains resistant to anthelmintics.
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