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Original Scientific Paper

NOVEL STRATEGIES FOR THE CONTROL OF GASTROINTESTINAL NEMATODES IN SHEEP

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Summary
Gastrointestinal nematodes are very important parasites of domestic animals, especially in small ruminants. In sheep, diseases usually have a subclinical form with a decrease in body weight and production, and sometimes there can be visible clinical symptoms such as anorexia, anemia, severe diarrhea and protein loss, all of which together can lead to death. Commercial drugs such as benzimidazole and macrocyclic lactones have been successfully used for decades to control these parasites. However, the irrational application of these drugs has led to the development of anthelmintic resistance, a decrease in their effectiveness and consequent economic losses that threaten the sustainability of sheep breeding. In addition, the use of commercial preparations is also associated with the residues in animal products and the environment, and there is also an increase in the price of these preparations. For this reason, novel strategies for controlling of these parasites are actively seeking, with the goal of establishing an integrated approach that involves the application of several different strategies. On the one hand, these include strategies for the rational application of commercial preparations based on refugia (targeted treatments, targeted selective treatments), as well as the combination and rotation of anthelmintics from different chemical groups. On the other hand, an integrated approach implies the use of different alternative strategies such as genetic selection of animals naturally resistant to nematodes, rational management of pastures, balanced nutrition with supplementary nutrients, biological control (use of fungi, bacteria, etc.), development of vaccines as well as the use of botanical preparations (plants and their products such as extracts and essential oils). Various

studies have proven the effectiveness of the mentioned strategies in the control of gastrointestinal nematodes of sheep, whereby the best results are achieved by their combined application. Thus, it is possible to slow down the development and spread of anthelmintic resistance, as well as achieve sustainable control of these parasites and reduce economic losses.

Key words: gastrointestinal nematodes, sheep, anthelmintic resistance, rational application of anthelmintics, alternative strategies, integrated control.

INTRODUCTION - GASTROINTESTINAL NEMATODES AND THE PROBLEM OF ANTIHELMINTIC RESISTANCE

Gastrointestinal nematodes represent one of the main obstacles to the development of modern sheep farming (Rodrigues et al., 2022; Bresciani et al., 2017). These parasites are distributed worldwide, as the genera *Haemonchus*, *Trichostrongylus*, and *Bunostomum* are characteristic for warmer climates, and *Teladorsagia*, *Nematodirus*, and *Cooperia* are typical for moderate climates (Mekonnen, 2021). With a high prevalence depending on the gender and area, they are also present in the territory of the Republic of Serbia (Kulišić et al., 2013; Pavlović et al., 2017). The diseases they cause in sheep are usually subclinical with reduced feed intake, loss of body weight and decreased production of milk, meat and wool (Bosco et al., 2020). However, in some cases, depending on the degree of infection, a clinically visible disease with signs of anemia, anorexia, diarrhea, large protein loss, anorexia, reduced immunity and fertility can occur, and in the case of a high load of parasites, a fatal outcome occurs (Giovanelli et al. , 2018; Beleckė et al., 2021). Therefore, these parasites can lead to economic losses in various ways, which include production losses, treatment costs, reduced fertility as well as deaths (Szewc et al., 2021).

Commercial preparations have been used for decades as the main tool for controlling gastrointestinal nematodes in small ruminants (Bosco et al., 2020). These include drugs from the group of benzimidazoles such as albendazole, fenbendazole and triclabendazole, macrocyclic lactones such as ivermectin, moxidectin and eprinomectin, as well as imidazothiazoles whose representatives are levamisole and tetramizole (Potârniche et al., 2021; Vineer et al., 2020). However, their effectiveness is increasingly declining due to the development of anthelmintic resistance, which has been reported in all drug classes, threatening the health and productivity of animals in different parts of the world (Fissiha and Kinde, 2021). Although it is considered that resistance is a natural phenomenon that occurs due to rare mutations (Shalaby, 2013), the role of veterinarians is primarily reflected in the speed of its development and spread. Thus, the main factors that contribute to the development of resistance are high frequency of treatment, prophylactic mass treatments, underdosing, continuous use of one drug and poor pasture management (Fissiha and Kinde, 2021; Falzon et al., 2014; Shalaby, 2013). An additional problem is the appearance of strains resistant to several groups of drugs, especially in H. *contortus*, *T. circumcincta* and *Trichostrongylus spp*., as well as the fact that the time required to develop resistance to a new drug, after its introduction to the market, according to some estimates, is less than 10 years (Fissiha and Kinde, 2021; Papadopoulos et al., 2012).

Although the exact amounts are not easy to determine, it is considered that the annual losses due to the development of anthelmintic resistance in various helminths at the European level is around 38 million euros, with a tendency to increase due to the increasing spread of resistant populations and the appearance of the aforementioned multi-resistant strains (Charlier et al., 2020; Vineer et al., 2020). Therefore, the detection and determination of the degree of development of resistance is extremely important for the development of strategies for its suppression, which implies the application and standardization of various *in vitro* tests such as the egg hatch test (EHT) and the larval development test (LDT), as well as *in vivo* tests such as the fecal egg count reduction test (FECRT) (Kebede, 2019; Mphahlele et al., 2019). Also, considering the frequency of their use in practice on the one hand, and taking into account consumer demand on the other, the use of commercial or synthetic drugs represents an increasing challenge from the aspect of residues that can contaminate food products such as meat and milk, as well as the environment (Castagna et al., 2022; Veerakumari, 2015). Finally, there is also the problem of increasing prices of these preparations such as albendazole and mebendazole on the world market observed in the last 10-15 years (Junsoo Lee et al., 2021).

From all mentioned above, it can be concluded that the independent use of commercial drugs in the treatment of parasitic infections is an increasingly less sustainable option. That is why novel strategies are based on the so-called an integrated approach that implies the use of several different strategies in order to achieve sustainable control of gastrointestinal nematodes of sheep, based on the rational application of commercial preparations on the one hand, and the use of various alternative options on the other hand. The aim of this paper is to present and describe these strategies, which could play a significant role in future approaches to the control of these parasites.

RATIONAL USE OF ANTIHELMINTICS

Strategies based on refugia

The term refugia means the percentage of the population of different developmental stages of the parasite in the pasture or in the households that avoids exposure to anthelmintics (Greer et al., 2020). In practice, refugia-based strategies aim to leave a certain number of parasites untreated, in order to slow down the spread of resistance. Namely, during the standard treatment of a certain herd of animals with the prescribed dose, the only parasites that will survive are the resistant ones that will then reproduce and pass on the resistance genes to the offspring, while the sensitive ones will be eliminated. This favors the selection of resistant parasites and their spread. Therefore, the application of refugia offers the possibility of leaving a certain number of susceptible parasites in the population, in order to allow the preservation of susceptible alleles. In this way, there is a cross between resistant and sensitive strains and a dilution of the frequency of resistant genotypes within a certain parasite population (Hodgkinson et al., 2019).

In various references (Calvete et al., 2020; Greer et al., 2020; Vineer et al., 2020) two basic strategies based on refugia are most often mentioned: *target treatments* (TT) and *target selective treatments* (TST). TT means treating all animals in a particular herd based on an assessment of the risk of parasitism. These treatments are given at the most appropriate time and serve to reduce the number of total treatments (i.e. increase the interval between them) to allow susceptible genotypes to establish in the pasture (Kenyon et al., 2009). On the other hand, TST are even more precise and are aimed at the treatment of only certain animals within the herd, which really require treatment due to clinical symptoms or a decrease in production, i.e. those that contaminate pastures the most (Calvete et al., 2020). If we take into account the characteristics of gastrointestinal nematodes of sheep, that within one herd of animals the largest number of these parasites (80%) is found in only 20-30% of the host (Bosco et al., 2020; Kenyon et al., 2009), treatments given to this way could really contribute to reducing the number of required treatments.

However, both TT and especially TST rely on the establishment of certain indicators that would determine at what time and which animals will be treated. According to Charlier et al. (2014) and Greer et al. (2020), depending on whether it is growing animals or adults, for TT these can be group *faecal egg count* (FEC), pepsinogen in plasma, body weight and growth, efficiency production, milk production, antibodies in milk and body condition score (BCS), and for TST individual egg count in feces, FAMACHA score, BCS (or the previous three listed in combination), diarrhea score, behavior, fecundity, etc. When talking about the mentioned indicators individually, FEC expressed in the number of *eggs per gram* of faeces (EPG) most directly indicates on the degree of infection in animals, whereby the eggs of gastrointestinal nematodes are relatively easy to determine compared to the eggs of other parasites. However, it is an intensive technique as the samples must first be sent to the laboratory and then analyzed (Preston et al., 2014; Kenyon et al., 2009). The FAMACHA score is a very good indicator and is based on a score (1-5) of the color of the conjunctival mucous membrane, in order to assess the degree of anemia caused by blood-sucking nematodes such as *H. contortus*, but the main limitation is that it consequently cannot be applied to other nematodes (Kenyon et al., 2009). Although BCS, measured on a scale of 1-5, as indicator of general condition and body reserves, is simple to apply, there is no general consensus about the threshold for treatment (Seyoum et al., 2017). The other indicators also have advantages and disadvantages, so there is more and more discussion about their combined application, e.g. FEC (with EPG less than 750) with FAMACHA score 4 or more or BCS 2 or less, as was done in sheep and goats in humid tropical conditions in Mexico, when 70% of unnecessary treatments were avoided (Soto-Barrientos et al., 2018; Torres-Acosta et al., 2014).

Combination and rotation of antihelmintics

The combination of anthelmintics involves the use of drugs from different chemical groups in order to slow down the development of resistance, and interest in this strategy has grown in the past few years (Fissiha and Kinde, 2021). Compared to the individual effect of anthelmintics, their combined use results in a synergistic effect, which leads to a significant increase in treatment efficiency. Application of this strategy in gastrointestinal nematodes of sheep is desirable for two reasons, on the one hand to enable sustainable control of nematodes in the presence of resistance, and on the other hand to delay the development of resistance to certain active substances in species where it is not yet evident (Shalaby, 2013). A combination of different anthelmintics could in practice restore the effectiveness of treatment on farms, which has been proven in certain studies (Ramos et al., 2018; Cezar et al., 2011). However, this strategy is effective only if the level of resistance is low, while at high levels it is unlikely to lead to the desired efficiency (Shalaby, 2013). Also, similar to conventional treatments, the question of the effect after long-term application of such combinations remains, given the resistance of nematodes to practically all classes of anthelmintics available today (Ramos et al., 2018). However, a computer-based model has shown that if the combination is administered when the drugs are first introduced, noticeable resistance will not develop for more than 20 years (Shalaby, 2013).

As previously stated, using one drug without rotation over a period of time is considered a high risk factor for the development of anthelmintic resistance, and this strategy can be used to prevent its development (Fissiha and Kinde, 2021). Therefore, there are certain recommendations to change different groups of drugs every one to two years, with the aim of prolonging the effectiveness of each of them and enabling the return of sensitivity in nematodes when the anthelmintic is not in use. However, there are some indications that this approach is effective only when resistance is at a very early stage of development and before it can be noticed, when natural selection could reduce the prevalence of resistant parasites. Given the degree of development of resistance to the most commonly used drugs, benzimidazoles and macrocyclic lactones, the success of this strategy is questionable in these groups (Abbott, 2017). Also, the previously mentioned model showed that this strategy leads to the development of resistance within 15-20 years (Shalaby, 2013).

ALTERNATIVE STRATEGIES

Selection of animals

Breeding sheep with greater resistance to infections caused by gastrointestinal nematodes is considered a promising strategy to reduce the use of anthelmintics (Aguerre et al., 2018). Namely, resistance to nematodes in small ruminants has low to high heritability (0.01 to 0.54), where the heritability of this feature indicates a potential genetic gain through selection. Therefore, it is considered possible to manipulate breeding lines in sheep in order to produce strong phenotypic differences (Zvinorova et al., 2016). Thus, it was shown earlier that the selection of animals with the lowest number of eggs in feces could be a selection criterion, considering that the FEC was reduced by 69% after the testing (Eady et al., 2003). Also, the degree of nematode burden can vary depending on the breed, as shown by the results of the study done by Goncalves et al. (2018), where Texel and Santa Inés had lower FEC compared to Ile de France and Dorper breeds. There is also an option to assess the genetic correlation between features that indicate body development (e.g. chest depth) and features that indicate the degree of parasitism and its consequences, whereby several different indicators should be used (Torres et al., 2021). However, genetic control approaches are difficult to implement in the systems of small production farms due to the lack of keeping the data record. Also, technical and infrastructural issues in genetic selection programs (small herds, poor infrastructure, etc.) should also be taken into account, especially in less developed countries (Zvinorova et al., 2016).

Pasture management

Adequate pasture management is also an effective way to control gastrointestinal nematodes and other parasites in ruminants (Kumar et al., 2013). This implies the application of several smaller strategies with the aim of avoiding the exposure of sheep to a high concentration of parasites that would lead to clinically visible diseases and a decrease in production, while on the other hand enabling the animals to develop immunity (Abbott, 2017). Ideally, clean or new pastures should be used, meaning those that have not been used for 6-12 months, pastures that have had a crop of hay or silage removed, pastures that are rotated with arable crops, and those that have recently been restored by tillage (Kumar et al., 2013). Pastures could be divided into plots, to allow a longer time before re-grazing (Shalaby, 2013). A larger amount of animals in a small space increases the concentration of parasites, which is why the optimal number of individuals per unit area should be used (Kumar et al., 2013). Some recommendations are 5 sheep, 5-7 goats or 1 cow per 4 m^2. Also, it is recommended to apply combined grazing of sheep and cows (not goats) or rotational grazing (Abbott, 2017). At the same time, it is necessary to regularly monitor the lawn in order not to overgraze and to maintain a productive pasture. Strategic deworming in early spring or at the beginning of the rainy season to remove newly emerged larvae before they contaminate the pasture (Shalaby, 2013), as well as using mature ewes in good condition after lambing to reduce contamination levels in high-risk pastures are some of the strategies that are also recommended (Abbott, 2017).

Nutrition management

Nutritional status can influence the resistance of sheep to gastrointestinal nematodes (Basabe et al., 2009). For this reason, as well as bearing in mind the fact that these parasites are integrated into the ruminant food chain, dietary manipulation can serve as a tool in the fight against them. A balanced diet provides an adequate source of nutrients (such as vitamins, minerals and proteins) and an acceptable load of parasites, which allows an optimal level of productivity. On the other hand, disturbances in this balance can lead to serious infections (Torres-Acosta et al., 2012). Thus, vitamins such as those from the A, D and B complex and minerals such as zinc, iron, cobalt, sodium, potassium and phosphorus are very important for the development of functional immunity against parasites (Kumar et al., 2013). In the absence of sufficient amounts of these substances in the pasture, supplementary feeding can be applied, which in addition to them also contains adequate amounts of protein, energy and other macro and micro ingredients. In this way, better animal resistance can be achieved and the use of commercial drugs can be reduced (Bresciani et al., 2017; Torres-Acosta et al., 2012). Therefore, the advantages of supplementary feeding include a reduction in the pathophysiological effects of parasitism, improved productivity, but also a reduction in natural infections (animals eat less food from the field and therefore ingest fewer larvae), as well as dilution of the number of nematode eggs in feces (the same or smaller amount of eggs in a larger amount of feces) (Torres-Acosta et al., 2012). Also, the direct or indirect anthelmintic effect of certain substances from natural or supplementary nutrients such as legumes rich in tannin should be taken into account (Bresciani et al., 2017; Torres-Acosta et al., 2012; Basabe et al., 2009).

Biological control

Biocontrol strategies include the use of natural enemies against gastrointestinal nematodes in order to reduce the number of free-living stages in pastures (Szewc et al., 2021). In this way, this method reduces the number of infectious stages (L_3) that are introduced into the animal's body by ingestion, with the aim of reducing the load of parasites to an acceptable level from the aspect of immunity. Biological control can be divided into direct, which involves the use of organisms that exert their effects directly on nematodes (fungi, bacteria, but also other nematodes), and indirect, which refers to the use of organisms whose behavior contributes to the destruction of habitats for parasites (earthworms and dung beetles) (Szewc et al., 2021; Worku et al., 2017; Kumar et al., 2013).

When it comes to direct biocontrol, nematophagous fungi, carnivorous species from the genera *Duddingtonia*, *Arthrobotrys* and *Monacrosporium* have been investigated the most. These fungi use sticky traps to catch nematodes, and they can be used in grain food or in the form of sodium alginate. It is important to note that the spores are activated and attack the larvae only after they are expelled through feces, which is why no harmful effects on the animal are expected. The most significant effect has so far been shown by the fungus *D. flagrans*, 37.6-91.5% depending on the study (Szewc et al., 2021). For this reason, there is already a commercially available preparation based on this mushroom in Brazl, which has shown *in vitro* effectiveness against gastrointestinal nematodes of sheep, but also cattle and horses (Rodrigues et al., 2022). Furthermore, some strains of *Bacillus thuringiensis* that produce the insecticidal δ-endotoxin have shown high *in vitro* efficacy against adult *H. contortus*, *T. colubriformis* and *O. circumcinta* (Worku et al., 2017; Kotze et al., 2005). Some free-living predatory nematodes such as *Butlerius butleri* and the mite *Lasioseius penicilliger* can also be used for direct biocontrol, although their lack of specificity should be taken into account. Other organisms include various viruses,

amoebas, protozoa, etc. (Szewc et al., 2021; Worku et al., 2017).
Dung beetles and earthworms that eat animal feces, contributing to the destruction of faecal points. In this way, they interfere with the development cycle of gastointestinal nematodes, and during feeding they can also swallow eggs and larvae. Also, they can be covered in the soil, especially dung beetles when forming and burying the balls. From the soil, the eggs and larvae will not return to the surface, and in this way their numbers are reduced (Szewc et al., 2021; Worku et al., 2017; Kumar et al., 2013). The positive effect of earthworms was already proven in the research by Waghorn et al. (2002), when their presence reduced the number of *T. circumcinta* by 63% in sheep.

Development of vaccines

Vaccines are considered a very attractive alternative strategy for the control of gastrointestinal nematodes in sheep, given that they are environmentally acceptable and less susceptible to the development of resistance by nematodes. Various studies in this field have been conducted in the past two decades, with the aim of identifying potential antigens for the development of a single or recombinant DNA vaccine (Ehsan et al., 2020; González et al., 2019). In *H. contortus*, the integral membrane glycoprotein H11 proved to be significant, with *in vivo* efficiency of over 75% (reduction of parasite load) and 90% (reduction of the number of nematode eggs in feces) (Nisbet et al., 2016). Based on this antigen, in combination with H-gal-GP, a vaccine was developed that is licensed for use in Australia, with a high effect in FECRT (>80%) and a high antibody titer, with two different nutritional regimens (Bassetto et al., 2018). Also, vaccination of six-month-old lambs with the somatic rHc23 antigen led to similar efficacy against *H. contortus*, whereby both humoral and cellular immune responses played a significant role in the protective response induced by this vaccine (González-Sánchez et al., 2018). A vaccine based on eight recombinant antigens identified in *T. circumcincta* was shown to be effective in stimulating significant levels of protection in lambs, but also in sheep in the peripartum period, with reduced FEC observed in vaccinated individuals (González et al., 2019). However, it is important to note that the genetic variations and immunoregulatory characteristics present in gastrointestinal nematodes hinder the development of vaccines, which requires the use of advanced molecular approaches. The aforementioned characteristics also imply that it will be very difficult to develop an effective *panspecies* vaccine, but that a vaccine against each species must be developed individually, as studies has shown (Britton et al., 2020; Ehsan et al., 2020).

Botanical control

Plants and their products have been used in the treatment of various diseases since ancient times. Nowadays, interest in phytotherapy has grown rapidly in both human and veterinary medicine, and one of the most frequently mentioned indications is various parasitic diseases. In this context, phytotherapy represents one of the most significant alternatives in the control of gastrointestinal nematodes in sheep (Štrbac et al., 2022a; Borges and Borges, 2016). In practice, plants can be used as whole, as their individual parts or products known as secondary metabolites (Hussein and El-Anssary, 2017). The classification of these metabolites is not simple considering their number and belonging to different chemical groups, but terpenes and their derivatives terpenoids, phenylpropanoids, flavonoids as well as the mentioned tannins are most often associated with anthelmintic activity (Jamwal et al., 2018; Hussein and El-Anssary, 2017). From some of these compounds, different herbal formulations with a rich chemical composition can be obtained, such as essential oils or extracts, which can be used against various parasites (Štrbac et al., 2023). In any case, in animals, botanical anthelmintics can be applied by intake by the animals themselves on pasture, by picking plants for animal feed and giving them in pens, as well as by producing the mentioned plant products (Alonso-Diaz et al., 2010).

The advantages of using botanical anthelmintics against gastrointestinal nematodes are multiple. Their rich chemical composition, which includes compounds from different chemical groups with various mechanisms of action, can contribute to high efficiency against different developmental stages of parasites, and on the other hand, to a lower susceptibility to the development of resistance compared to commercial preparations (Štrbac et al., 2023; Borges and Borges, 2016). Thus, the *in vitro* and *in vivo* effect of numerous essential oils as well as plant extracts against various gastrointestinal nematodes of sheep has been proven, and some of the most significant results were obtained for oregano, thyme, sea buckthorn, fennel, various types of eucalyptus, mint, lemon grass, etc. (Štrbac et al., 2022b, Štrbac et al., 2022c; Andre et al., 2018), and in some tests, their individual isolated active ingredients such as carvacrol, thymol, anethole, carvone, etc., proved to be effective (Katiki et al., 2017). Furthermore, their natural origin is often associated with smaller amounts of residues in animal products such as meat and milk, as well as in the environment (Štrbac et al., 2023; Veerakumari, 2015). Finally, there is also a financial aspect, given that in most cases herbal formulations are associated with suitable prices, especially in countries with developed biodiversity (Ferreira et al., 2018).

However, the application of botanical anthelmintics against gastrointestinal nematodes has not yet been totally implemented due to the still insufficient number of tests and confirmation of their effectiveness and safety in animals, although the number of such studies has been increasing in the last few years (Štrbac et al., 2022a; Štrbac et al., 2022c; Andre et al., 2018). Also, in previous tests, the *in vivo* efficiency was usually lower compared to commercial preparations due to various factors that can affect their field efficiency, but this problem can be overcome in different ways, including the application of encapsulation techniques, as has been proven in different studies (Ali et al., 2021; Mesquita et al., 2013). In any case, plant products, considering the numerous advantages mentioned, could be successfully used in integrated approaches to the control of different parasites.

INTEGRATED CONTROL APPROACH

Bearing in mind all the above, it is clear that each of the mentioned strategies, both those related to the rational application of commercial preparations and alternative ones, has certain advantages and disadvantages. For this reason, it seems that the independent application of none of the mentioned strategies is sustainable on its own, but that the best effect could be achieved with an integrated approach, i.e. their combined application (Szewc et al., 2021), and there are numerous examples of this. Thus, study done by Shalaby et al. (2012) proved that ivermectin in combination with *Nigela sativa* oil has better efficiency, observed from the morphological aspect and ultrastructural damage, against *H. contortus*, but also the tapeworm *Moniezia expansa* and the fluke *Fasciola gigantica* compared to its independent application. Similarly, in the study done by Marjanović et al. (2020) and Trailović et al. (2015), it was shown that the combination of carvacrol in combination with nicotinic acetylcholine receptor agonist drugs such as imidazothiazole, or GABA receptor agonist drugs such as avermectin and piperizan could have a synergistic effect against various nematodes, considering the results obtained on the neuromuscular preparation of *Ascaris suum*. Furthermore, in the study done by Vilela et al. (2018), the effect of a combination of pellets based on the nematophagous fungus *D. flagrans* and levamisole hydrochloride (5%) against gastrointestinal nematodes of sheep was tested. The results showed a synergistic effect of the mentioned combination, and the group of animals that received both treatments had the lowest EPG values in all time intervals of observation, compared to the group that received only the chemical preparation, as well as to the control group.

The combined application of several different alternatives, such as nutrition rich in condensed tannins and the selection of resistant animal breeds, was tested.

Although the additive or synergistic effect of this combination was not clearly demonstrated, the proportion of 55% sainfoin in the diet led to a significantly lower EPG compared to the control diet (Werne et al., 2013). In the study done by Bambou et al. (2021), the effect of the application of combined grazing of kids and heifers and supplementary feeding with forage tropical grasses on the response to the presence of gastrointestinal nematodes and production characteristics in kids was examined. It was shown that both individual strategies had a positive effect (FEC significantly lower in the group of combined grazing, and cell volume - PCV, BCS and live weight in the group that received supplements), but that their combination would improve the production performance of the animals. From all these examples it is clear that the number of possible combinations of different strategies for the control of gastrointestinal nematodes in sheep is large, which provides different opportunities to find the most effective, safest and most practical. However, the task is not simple and requires numerous tests, but it seems to be the only way for sustainable control of gastrointestinal nematodes in sheep in the future.

CONCLUSION

The standard application of commercial preparations in the control of gastrointestinal nematodes of sheep is becoming less and less a sustainable approach with regard to the development of resistance in nematodes, as well as due to other reasons (residues and increasing prices). That is why, recently, a lot of work is being done on defining and developing new strategies, which can be classified into two groups: the rational application of commercial preparations and the introduction of different alternative methods. Each of the strategies mentioned in this paper from any of the mentioned groups has certain advantages, as has been proven in various studies. Nevertheless, bearing in mind certain limitations of these strategies, it seems that the best effect could be achieved by their combined application. In this way, sustainable control of sheep gastrointestinal nematodes and other parasites could be achieved through integrated control in the future.

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