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Research article

Caprine roundworm nematode resistance to macrocyclic lactones in Northeastern Thailand

Sarinya Rerkyusuke[1,*], Pichayawadee Lamul[2], Chanoknan Thipphayathon[2], Kamonwan Kanawan[2] and Sarthorn Porntrakulpipat[1]

[1]Division of Livestock Medicine, Faculty of Veterinary Medicine, Khon Kaen University, Khon Kaen 40002 Thailand
[2]Faculty of Veterinary Medicine, Khon Kaen University, Khon Kaen 40002 Thailand.

Abstract

Roundworm nematodes are a significant problem in goat meat farming worldwide. These parasites can cause production losses, reduce feed efficiency and compromise animal health and welfare. Macrocyclic lactones (MLs) are common anthelmintic drugs to treat roundworm nematode infection in livestock. The objective of study was to detect roundworm resistance to MLs in meat goats in Northeast Thailand. One hundred and nineteen goats from 6 herds were studied from June to December 2022. Each herd was randomly allocated to control (n=21), eprinomectin (n=34), ivermectin (n=40) and moxidectin (n=24) groups. Anthelmintic resistance (AR) was assessed based on the Fecal Egg Count Reduction Test (FECRT) and larva culture at pre-treatment (D0) and 14 days post-treatment (D14). Prevalence of Strongyle nematodes and *Trichuris* spp. infection was 100% (6/6 herd), and 66.7% (4/6 herd), respectively. The number of Strongyle eggs was significantly reduced in the eprinomectin group ($p < 0.01$). In contrast, the ivermectin group was significantly increased ($p < 0.01$). The prevalence of ML resistance of Strongyle nematodes and *Trichuris* spp. was 83.3% (5/6 herd) and 25.0% (1/4 herd), respectively. The dominant larva was *Haemonchus contortus* at pre- and post-treatment in every herd. This study demonstrated the presence of ML resistant Strongyle nematodes as *H. contortus* and *Trichuris* spp. in this area. To reduce ML resistance it can be useful to use drugs in combination or rotate MLs with other classes of anthelmintics or in targeted treatment programs and integrated parasite management strategies. Consequently, the efficacy of anthelmintic drugs in small ruminants needs to be monitored and surveilled in this area.

Keywords: Macrocyclic lactones, resistance, roundworm, nematodes, caprine.

Corresponding author: Sarinya Rerkyusuke, Division of Livestock Medicine, Faculty of Veterinary Medicine, Khon Kaen University, Khon Kaen 40002 Thailand. Tel: +664-320-2404, E-mail: sarinyare@kku.ac.th

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INTRODUCTION

The population of meat goats in Northeast Thailand has been increasing in recent years due to a variety of factors (ICT DLD, 2018-2023). One of the main reasons is the growing demand for goat meat in local and regional markets. Goat meat is a popular protein source in many countries, including Thailand, and its consumption has been increasing due to changing dietary preferences and the perception that it is a healthy and lean meat. In addition, the production of meat goats in Northeast Thailand is also being driven by the availability of suitable land for grazing and the relatively low input costs associated with goat production. Goats are well-suited to grazing on marginal land that is not suitable for other types of livestock, and they require relatively low levels of inputs such as feed and water.

Gastrointestinal (GI) parasites are common health problems in goats, including nematode, cestode and trematode (Smith and Sherman, 2009). In particular, Strongyle nematodes are parasites that can cause significant damage to the gastrointestinal tract, leading to poor growth, weight loss, anemia and reduced milk production. The most common types of Strongyle nematodes in goats include the small intestinal Strongyles (e.g. *Haemonchus contortus*, *Trichostrongylus* spp., *Cooperia* spp., *Nematodirus* spp.) and the large intestinal Strongyles (e.g. *Oesophagostomum* spp.). *H. contortus*, also known as the barber pole worm, is a blood-sucking parasite that can cause severe anemia and death in goats (Bowman, 2009). It is one of the most economically important parasites of small ruminants worldwide, and its control is a major challenge for goat producers. GI parasite infected goats can experience a range of symptoms, including poor growth, weight loss, diarrhea, anemia and even death in severe cases.

Strongyle infections in goats are typically diagnosed through fecal egg counts, which involve examining the number of Strongyle eggs present in a goat's feces (Bowman, 2009). Treatment for Strongyle infection typically involves the use of anthelmintic drugs, such as macrocyclic lactones (MLs), benzimidazoles and imidazothiazoles (Smith and Sherman, 2009).

MLs are a class of anthelmintic drugs commonly used to treat gastrointestinal parasitic infections in meat goats. MLs work by binding to specific receptors in the parasites, leading to the paralysis and death of the worms (Prichard and Geary, 2019). MLs bind to and activate a specific receptor, such as the gamma-aminobutyric acid (GABA) receptors in nematode *H. contortus* (Brown et al., 2012). GABA is a neurotransmitter that plays a key role in regulating the activity of neurons in the nervous system. MLs bind to a site on the GABA receptor complex, enhancing the binding of GABA to the receptor and increasing the flow of chloride ions through the channel. This leads to hyperpolarization of the neuron, reducing its excitability and resulting in paralysis of the invertebrate (Brown et al., 2012). In addition, the glutamate-gated chloride channel (GluCl) receptor is a type of ligand-gated ion channel found in the nervous system and muscles of many invertebrates and some vertebrates. When activated by MLs, the GluCl receptor opens a chloride ion channel, leading to hyperpolarization of the cell membrane and inhibition of nerve transmission or muscle contraction. In nematode *H. contortus*, MLs act on the GluCl receptors present in muscle and nerve cells, leading to paralysis and death of the parasites (Atif et al., 2017).

The three most common MLs used in veterinary medicine are ivermectin, moxidectin and eprinomectin that is effective against a broad range of parasites, including roundworms, lungworms, mites and lice. Ivermectin is commonly used in livestock and horses, as well as in dogs and cats. Moxidectin is a newer ML. It has a longer duration of action than ivermectin, and is commonly used in cattle, sheep and horses. Eprinomectin is another broad-spectrum antiparasitic drug. It is commonly used in cattle and has a long duration of action, making it a popular choice for controlling parasites in grazing animals.

However, the overuse of MLs has led to the emergence of resistance in some roundworm species, making it more difficult to control parasitic infections in goats. Roundworm resistance to MLs, particularly in small ruminants, can significantly impact animal health and productivity; these forces are a growing concern in many regions of the world (Vicker et al., 2001; Veale, 2002; Hinney et al., 2022; Wondimu and Bayu, 2022). Additionally, There is no information on the resistance of roundworms to MLs in meat goats.

The objective of this study was to identify the resistance of roundworms to MLs in meat goat herds in Chaiyaphum and Khon Kaen, Thailand. Overall, the goal of such a study would be to provide valuable information to goat producers and veterinarians about the prevalence and potential impact of MLs resistance in meat goats, and to help inform the development of effective GI-parasites management programs.

MATERIALS AND METHODS

Study area and design

The study was conducted from June to December 2022 in Chaiyaphum province (16° 20' 30.8" N 102° 24' 01.3" E) and Khon Kaen province (16° 28' 54.9" N 102° 29' 39.1" E) in Thailand, due to the crowding of meat goat herds in the Northeast (ICT DLD, 2022). Topographically, the study area is at an altitude of 180 to 200 meters above sea level. The minimum and maximum annual temperatures range from 12.0 ^{o}C to 26.0 ^{o}C and 22.0 ^{o}C to 39.6 ^{o}C, respectively. The mean annual rainfall is 4.7 to 5.1 mm. The relative humidity varies between 62 and 80% (Upper Northeastern Meteorological Center, 2022).

Study Animals

Inclusion criteria included animals aged over 4 months; both sexes and different ages were used. Generally, healthy goats were used to identify the Gastrointestinal parasite nematodes. All herds withdrew the anthelmintic at least 1 month before the investigation. In total 119 animals in 6 small-holder meat goat herds (Chaiyaphum 2 herds and Khon Kaen 4 herds) were included. The animal study protocol was approved by the Institutional Animal Care and Use Committee, Khon Kaen University (record no. IACUC-KKU-43/65, date of approval 25 May 2022).

Experimental Design

All goat herds were small-holder meat goat herds. The goats in herds ranged from 50 to 80 heads per herd. For feed management, generally, farmers cut and carry the leaf of *Leucaena leucocephala,* or give corn silage to their animals together with 16% protein concentrate feed. All farmers have their own pastures and allow animals to graze on pastures from 10.00 am to 4.00 pm without rotating grazing areas.

Each herd was randomly assigned to a group, including control (untreated) (n=21), eprinomectin treated (dose 0.2 mg/kg, subcutaneous route) (n=34), ivermectin treated (dose 0.2 mg/kg, subcutaneous route) (n=40), and moxidectin treated (dose 0.2 mg/kg, pour-on topical route) (n=24). For the treatment group, all animals had their body weight measured by hanging from a digital balance before calculating the correct dosage of the deworming drug. Feces were sampled pre-treatment (D0) and 14 days post-treatment (D14). Anthelmintic resistance was assessed based on the Fecal Egg Count Reduction Test (FECRT) method following the guidelines of the World Association for the Advancement of Veterinary Parasitology (WAAVP) (Coles et al., 2006). FECRTs was performed only on goats with EPG ≥ 50 at pre-treatment.

Fecal samples and examination

Feces samples were collected directly from the rectum of each animal. At least 5 g of fresh feces from each animal was placed in a plastic bag. All samples were stored at 4°C during transportation to the laboratory. The fecal egg count and identification of worm modification method from Brummaier et al. (2021) was used. Briefly, 2 g of individual feces samples were mixed with 10 ml of 10% formalin solution until suspended. Then, the sample was filtered through a sieve with a pore size of 0.6 mm. The parasite eggs were passed through a strainer conical tube and then the sample was centrifuged at 1,500 rpm for 5 min. The supernatant was discarded, and the remaining deposit was resuspended with 6 ml of 10% formalin and 4 ml of ethyl acetate. The solution was strongly shaken for 30 s or until homogenised. The solution was then centrifuged at 1,500 rpm for 5 min. The supernatant was then gently discarded, and a few of the lowest layers, which were sediment egg worms, thus remained.

Identification of egg worms and their morphology differentiation was conducted following the previously described protocol by Taylor et al. (2016). For the microscopic examinations, 3 drops were taken from the tip of a conical tube of suspension and prepared on a glass slide. The fecal sample was examined at 400x magnification, and the number of eggs and the type of parasites were determined. The number of eggs per gram (EPG) was calculated by the average eggs multiplied by the number of drops in the suspension and divided by the mass of feces in grams (Aunpromma, 2013).

Coproculture and larva identification

Feces from an individual herd and group of treatment were pooled and cultured for larval identification. At least 50 grams of individual feces samples from each herd and each group were pooled in sterile plastic bags and added to sterile litter at a ratio of 1:1 and moistened by distilled water. The pooled feces were incubated at ambient temperature of approximately 25–35°C for 14 days in a dark box. After incubation, all third-stage larvae were harvested using the modified Baermann technique for 24 h. Third-stage larvae were harvested using a 15 ml conical tube and identified using the standard key for morphological features. At least hundreds of L3 larvae were fixed with

1-2% formalin and heating for a minute, identified morphologically, revealing a differentiated species/genus of GI nematodes (Van Wyk et al., 2004). Other nematode species, such as *Trichuris* spp., were not identified in this step.

Statistical Analysis

Data were analyzed using Microsoft Excel, GraphPad Prism 9.0 for Windows (version 9.0.0). The normal distribution was determined using the Shapiro–Wilk test. Most of the data had a value of $p < 0.05$ according to the Shapiro–Wilk test and were not a normal distribution; nonparametric tests were used for statistical analysis.

The paired *t-test* was used to compare the difference of nematode eggs within the same group at pre- and post-treatment ($p < 0.05$). Two-way ANOVA was used to compare the differences in nematode eggs between groups at pre- and post-treatment ($p < 0.05$).

FECRs was calculated between pre- and post-treatment following McKenna (2006) as FECRT% = 100 x (1-[T2/T1]) where T1 is the number of EPG pre-treatment and T2 is the number of EPG post-treatment.

Interpretation of treatment effectiveness was that FECRs ≥ 95% was treatment effective, no evidence of resistance, FECRS ≥ 90% and < 95% was reduced efficacy and suspected resistance, FECRS ≥ 80% and < 90% was reduced efficacy and resistance is likely, while FECR < 80% was ineffective and resistance is highly likely (Voigt et al., 2022).

RESULTS

All herds were infected with roundworm nematodes as Strongyle. Only four herds were infected with *Trichuris* spp. roundworm. The number of Strongyle eggs and *Trichuris* spp. eggs were not significantly different between the groups at pre-treatment ($p > 0.05$).

For Strongyle eggs, post-treatment, there was only a significant decrease of Strongyle eggs in the eprinomectin group ($p < 0.01$). Surprisingly, the number of Strongyle eggs increased in the ivermectin group ($p < 0.01$). Post-treatment, the number of Strongyle eggs in the ivermectin group was significantly different between the control group ($p < 0.01$) and the eprinomectin group ($p < 0.0001$). The results are shown in Figure 1.

For *Trichuris* spp. eggs, the eprinomectin and ivermectin groups had a reduction in eggs post-treatment. However, the number of control and treatment groups was not significantly different post-treatment ($p > 0.05$). The results are shown in Figure 1.

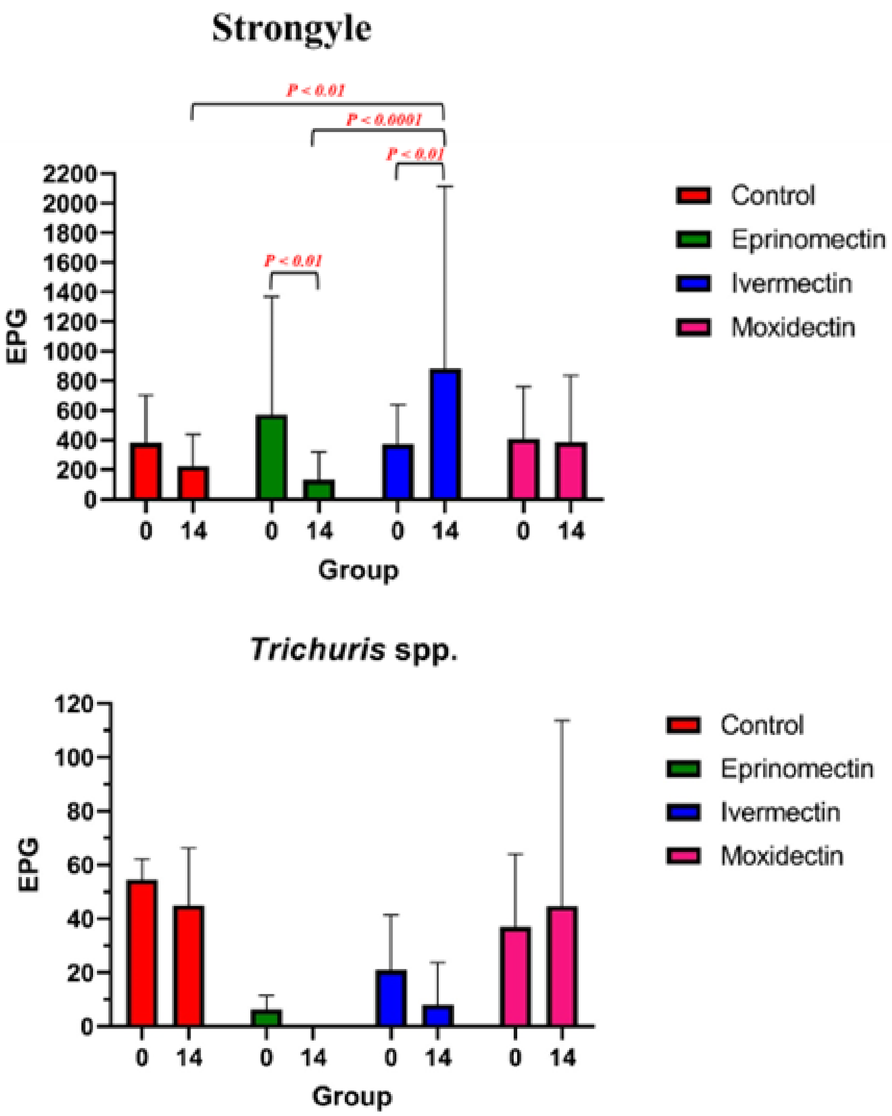

Figure 1 Number of Strongyle eggs and *Trichuris* spp. eggs pre- and post-treatment in each group.

The efficacy of MLs against Strongyle nematode indicated Strongyle resistance due to the percentage of FECRT being less than ninety percent in the three groups of treatment. However, the eprinomectin group had the highest percentage when compared with the ivermectin group and the moxidectin group (Figure 2).

MLs were effective against the *Trichuris* spp. due to the percentage of FECRT being more than ninety percent in the eprinomectin group. However, the ivermectin and moxidectin groups were inefficient, due to the FECRT being less than ninety percent. The results are shown in Figure 2

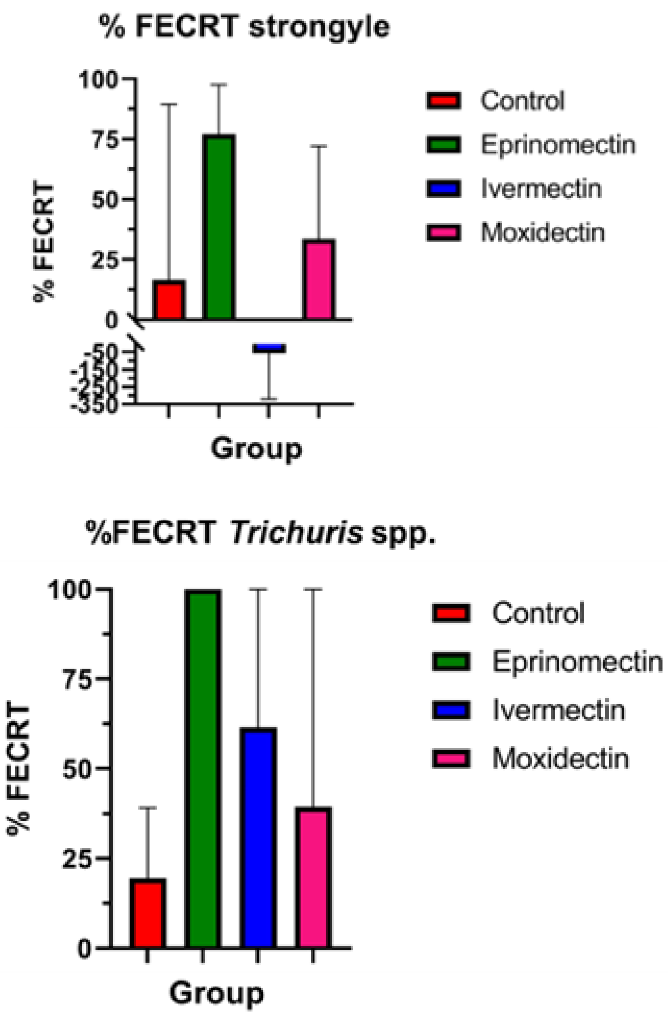

Figure 2 % FECRT of Strongyle eggs and *Trichuris* spp. eggs in each group.

In this study, only one herd showed Strongyle nematodes susceptible to eprinomectin and ivermectin, but other herds were resistant. % FECRTs of Strongyle nematodes for eprinomectin, ivermectin and moxidectin in the 6 herds are shown in Table 1, while % FECRTs of *Trichuris* spp. for eprinomectin, ivermectin and moxidectin in 4 herds are shown in Table 2.

Larva culture was dominated by *H. contortus* larva, followed by *Trichostrongylus* spp. and *Strongyloides* spp. in every herd at pre-treatment in every group (Table 3). Post-treatment the *H. contortus* larva still dominated in all groups and herds.

Table 1 % FECRT of Strongyle nematode for eprinomectin, ivermectin and moxidectin in 6 herds

Farm	Eprinomectin					Ivermectin					Moxidectin				
	Mean	Lower 95%CI	median	Q1	Q3	Mean	Lower 95%CI	median	Q1	Q3	Mean	Lower 95%CI	median	Q1	Q3
A	**56.5***	**-9.4**	**61.9**	**14.4**	**93.1**	NA	NA	NA	NA	NA	**42.55***	**-7.3**	**49.5**	**9.8**	**68.3**
B	**41.4***	**-9.5**	**77.5**	**36.9**	**87.5**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
C	**-15.0***	**-142.7**	**-0.4**	**-98.2**	**53.6**	**-144.4***	**247.9**	**-60.4**	**-321.7**	**34.1**	**-85.9***	**-242.0**	**16.6**	**-18.7**	**77.1**
D	99.3	97.6	100.0	98.2	100.0	100.0	NA	100.0	NA	NA	NA	NA	NA	NA	NA
E	NA	NA	NA	NA	NA	**83.8***	**57.1**	94.0	87.1	100.0	NA	NA	NA	NA	NA
F	**65.2***	**22.7**	**85.3**	**31.9**	**100.0**	**-445.0***	**-793.8**	**-162.5**	**-698.7**	**-81.2**	NA	NA	NA	NA	NA

NA = Not applicable due to EPG being less than 50; * Strongyle resistant to anthelmintic drug

Table 2 % FECRT of *Trichuris* spp. for eprinomectin, ivermectin, and moxidectin in 4 herds

Farm	Eprinomectin					Ivermectin					Moxidectin				
	Mean	Lower 95%CI	Median	Q1	Q3	Mean	Lower 95%CI	Median	Q1	Q3	Mean	Lower 95%CI	median	Q1	Q3
A	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	100	NA	100.0	NA	NA
B	100.0	NA	100.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
C	NA	NA	NA	NA	NA	**-19.4***	**-210.8**	100.0	-142.5	100.0	**-349.6***	**-1672.6**	**48.6**	**-1192.2**	**94.8**
F	100.0	NA	100.0	NA	NA	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA

NA = Not applicable due to EPG being less than 50; * *Trichuris* spp. resistant to anthelmintic drug

Table 3 Proportion of Strongyle larvae at pre- and post-treatment in each group and herd

Farm	Day	Control			Eprinomectin			Ivermectin			Moxidectin		
		HC	TS	SP	HC	TS	SP	HC	TS	SP	HC	TS	SP
A	0	76	1	23	74	4	22	NA	NA	NA	86	2	12
	14	57	6	37	70	23	7	NA	NA	NA	62	32	6
B	0	76	7	17	86	6	8	NA	NA	NA	NA	NA	NA
	14	58	32	10	83	14	3	NA	NA	NA	NA	NA	NA
C	0	63	22	15	55	26	19	63	22	15	63	25	12
	14	59	5	36	74	19	7	68	19	13	59	25	16
D	0	NA	NA	NA	51	1	48	0	0	100	NA	NA	NA
	14	NA	NA	NA	41	4	55	70	3	27	NA	NA	NA
E	0	NA	NA	NA	NA	NA	NA	72	13	15	NA	NA	NA
	14	NA	NA	NA	NA	NA	NA	69	5	26	NA	NA	NA
F	0	NA	NA	NA	30	57	13	80	5	15	NA	NA	NA
	14	NA	NA	NA	80	16	4	78	4	18	NA	NA	NA

HC = *Haemonchus contortus*; TS = *Trichostrongylus* spp.; SP = *Strongyloides* spp.; NA = Not applicable due to EPG being less than 50

DISCUSSION

In the present study, the prevalence of roundworm parasites was a hundred percent in every herd. The Strongyle nematode commonly found was *H. contortus*, which related to the high prevalence of ML resistance based on the results from % FECRT and larva identification post-treatment. Similarly, Mickiewicz (2021) in Poland and Ratanapob (2022) in Sing Buri province, Thailand have also reported high levels of ML resistance in small ruminants. This study was the first report of the roundworm nematode *H. contortus* having resistance to MLs in Northeastern Thailand.

Interestingly, ivermectin resistance in roundworm herds may present resistance to moxidectin and eprinomectin as well. This might be due to the ivermectin having been a common endectocide for livestock animals such as cattle, sheep and goats in Thailand since 1991 (Chaisanabunthid et al., 2003). Moreover, farmers generally used single anthelmintic drugs for their adult animals; some roundworm populations may develop genetic mutations that allow them to resist the effects of these drugs. When this happens, the roundworms are said to be "resistant" to the drugs (Gilleard, 2013; Tuersong et al., 2022). The study of Paraud et al. (2016) has similarly shown that when roundworms develop resistance to ivermectin, they may also become resistant to other ML drugs, such as moxidectin. This is because these drugs have similar modes of action and can bind to the same receptors in the roundworm's nervous system (Prichard and Geary, 2019).

The route of administration of MLs was subcutaneous injections for eprinomectin and ivermectin. Only moxidectin is a pour-on formulation. For controlling and treating GI parasites, injectable or oral drench formulations of moxidectin may be more effective against a broader range of Strongyle nematodes, due to the pour-on route having less absorption than oral and subcutaneous routes (Baynes et al., 2000). That the efficacy of moxidectin seems to be less in this study may be from using the topical route.

The findings of this investigation underscore the importance of responsible use of anthelmintic drugs and integrated parasite management strategies to help reduce the risk of drug resistance. This can include strategies such as targeted treatment based on fecal egg counts, pasture management such as pasture rotation and mixed-species grazing can reduce the parasite burden by interrupting the life cycle of the parasites and diluting the number of infective larvae in the pasture, changing different classes of anthelmintic drugs or using a combination of anthelmintic drugs, genetic selection for resistance to parasites, avoiding treating does around the kidding period, and avoiding underdosing (Van Wyk and Bath, 2002; Van Wyk et al., 2004; van Wyk et al., 2006; Learmount et al., 2015; Bollinger et al., 2016). An experimental study of MLs resistance in *H. contortus* recommended that a 5- to 10-fold intraruminal dose of ivermectin can improve efficacy against *H. contortus* resistance to ivermectin (Alvarez et al., 2015).

Based on the study of Jouffroy et al. (2023), it was shown the molecular technique to identification and quantification of eprinomectin-resistant larvae and high-performance liquid chromatography (HPLC) with fluorescent detection of drug concentration in serum which related to the route of drug administration. However, the limitation of this study was not to identify and detect the resistant gene larvae, and the lack of HPLC analysis and effective drug concentration in goat serum related to the drug administration route. This might need further study.

CONCLUSIONS

The current study shows the high prevalence of MLs resistance in roundworm nematodes in Northeast Thailand. *H. contortus* was the dominant nematode-developed resistance to MLs. Once *H. contortus* has developed resistance to several classes of MLs such as ivermectin, it is also likely to have reduced susceptibility to moxidectin and eprinomectin as well. It is important to note that while resistance to these drugs is a concern, they are still effective against many parasite species and can be useful in combination with other treatments or in targeted treatment programs. In addition, there are other classes of anthelmintics, such as benzimidazoles and imidazothiazoles, that can be used in rotation with MLs to help reduce the risk of resistance. Therefore, the efficacy of anthelmintic drugs needs to be monitored and surveilled in this area.

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AUTHOR CONTRIBUTIONS

Sarinya Rerkyusuke: Conceptualization and Study design, Formal analysis, Investigation, Data curation, Statistical analysis, Writing—original draft preparation.
Pichayawadee Lamul: Formal analysis, Investigation.
Chanoknan Thipphayathon: Formal analysis, Investigation.
Kamonwan Kanawan: Formal analysis, Investigation.
Sarthorn Porntrakulpipat: Investigation, Writing—original draft preparation. All authors reviewed the results and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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