



Anthelmintic Efficacy and Pharmacodynamic Effects of Levamisole Oxcyclozanide Combination as (Levanide®) in Fattening Calves

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Thirty calves of one-year old and body weight (BW. = 152.5±2.0 kg) had been confirmed for presence of mixed infection of different internal parasites like *Fasciola gigantica*., *Paramphistomum microbothrium*., and (*Trichostrongylidae spp.*). These calves were used to evaluate the anthelmintic efficacy, growth performance, haemato-biochemical and serum antioxidant parameters of single oral administration of levanide® (levamisole (LEV)-oxyclozanide (OXY) combination as active principles) in a dose of 2.5 ml of the product /10 kg BW. The fecal egg count reduction test (FECRT) for the tested animals showed a significant (P<0.05) reduction in eggs per gram of feces for the examined parasites on 3rd day then on the 7th day post-treatment in comparison with pretreatment samples with a 100% anthelmintic efficacy. The growth parameters, and red blood corpuscle count (RBCs) were significantly (P<0.05) improved post-treatment compared to pretreatment measures. A slight reversible elevation of serum aspartate aminotransferase (AST) level was noticed on the third day to the 7th day after administration followed by a decrease in its activity till the end of the experiment. The total antioxidant capacity (TAC) was decreased from day 7 to the end of the trial; glutathione-S-transferase (GST) showed a slight decrease in activity after drugs administration followed by a marked rise (p < 0.05) in its activity on days 14 and 28. Accordingly, it could be concluded that administration of the LEV-OXY active principals combination is a successive, efficient and safe anthelmintic with minimal side effects that could help in increasing growth performance.

Keywords: Anthelmintic Efficacy, levanide® (Levamisole-Oxyclozanide), Growth Performance, Haemato-Biochemistry.

Introduction

Internal parasitic infection is one of the most important problems affecting farm animal's production all over the globe because of its retarding effect on the productivity of animals [1,2]. Acute infection of ruminants with *Fasciola* species is associated with acute hepatic cirrhosis

and subsequent hepatic failure. While the chronic form is more common and usually associated with milk, weight gain loss, and fertility problems which collectively have a severe economic impact on the industry [3,4]. One of the most common parasitic diseases is Paramphistomiasis, which has a wide geographical distribution in subtropical

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and tropical areas. Upward migration of immature worms in small intestine mucosa mainly in the duodenal mucosa causes severe enteritis, followed by anorexia, unthriftiness, severe diarrhea, and subsequently polydipsia, dehydration, and mortality in the severely affected cases could occur [5]. Nematodes infections are more common in ruminants and are usually associated with gastroenteritis, diarrhea, poor food conversion, and weight loss. Therefore, developing effective control programs is mandatory to increase the productivity of the animals [6].

The administration of combined anthelmintic therapies against nematodes and trematodes is a commonly used strategy to broaden the spectrum of efficacy and decrease the load of frequent administration on livestock. Previous reports cleared that routinely administering anthelmintics at predetermined times of the year with the optimum doses induces the destruction of the parasite life cycle, which effectively aids in the control of ruminant internal parasites [7,8].

One of the most commonly used anthelmintic combinations all over the world and particularly in Egypt is levamisole (LEV) with oxcyclozanide (OXY) [9,10]. Therefore, this study was designed to study the anthelmintic efficacy of levanide® (LEV-OXY combination) on the different internal parasites affecting yearling cattle calves in the Behera governorate of Egypt with special reference to their pharmacodynamic effects on growth performance, haemato-biochemical and serum antioxidant levels.

Material and Methods

Ethical Approval All the experiments and usage of farmer's animals were conducted according to the recommendations and guidelines of the Institutional Animal Ethics Committee, Faculty of Veterinary Medicine, Alexandria University, Alexandria, Egypt (205/2023).

Animals

This study was carried out on a private small-scale beef cattle farm in Behera governorate in Egypt (30°50'53.16"N, 30°20'36.78"E). Thirty male yearling cattle calves of body weight (BW) range (140-160 kg mean, 152.5±2.0) were selected for this study. Based on the initial fecal examination, it was found that all animals were suffering from a mixed infection with the different parasites. But collectively, *Fasciola gigantica* was recorded in 18 out of the total 30 calves (18/30), *Paramphistomum microbothrium* was recorded in

14 calves out of the total 30 calves (14/30), and (*Trichostrongylidae spp.*) in 24 out of the total 30 calves (24/30). All animals were kept in the same conditions and dry ration.

Drug and Chemicals

Levanide® Oral Suspension (ATCO Pharm. Co. Egypt) each ml contains (30 mg Levamisole hydrochloride base and 60 mg Oxcyclozanide as active principals) was used at the recommended manufacturer dose (2.5 ml of the product/10 kg body weight (BW)). Chemicals and kits used in hematological, biochemical, and serum oxidative biomarkers were purchased from Vitroscent Co., Egypt, Spain react Co., Egypt and Ranbut; Randox Laboratories, Antrion, United Kingdom, respectively.

Experimental Design

Thirty male yearling calves represented all animals in the study ($n=30$). Growth performance parameters including BW, body weight gain (BWG), food intake (FI), and food conversion rate (FCR) were estimated through three weights during 2 months; one month before and one month after the anthelmintic product administration. At 0 day, and at 3, 7, 14, and 28-days post-drug administration, fecal, two blood samples were collected by jugular vein puncture. The first blood sample was collected in vacutainer tubes with EDTA and used for evaluation of the hematological parameters which was done within 2 hours after sample collection fig. (1). The second blood sample was taken in a plain centrifuge tube for serum separation. Sera were stored at -20 °C until used for biochemical analysis. The fecal samples were investigated by sedimentation and floatation techniques to determine the fecal egg count. Based on the manufacturing recommendation dose, the tested anthelmintic product was singly orally administered to each calf in a single dose according to its body weight.

Evaluation of Growth Parameters

Calves were weighed individually three times one month before the treatment, at the time of treatment (0 day) and one-month post-drug administration. While the live body weight change was taken as a measure of growth. The BWG (expressed in kilograms) was calculated as the difference between each of the two successive weights. Feed intake was estimated and provided daily per calf for estimation of the FCR by dividing the amount of dry matter intake in kilograms during a month by BWG in kilograms during the same period [11].

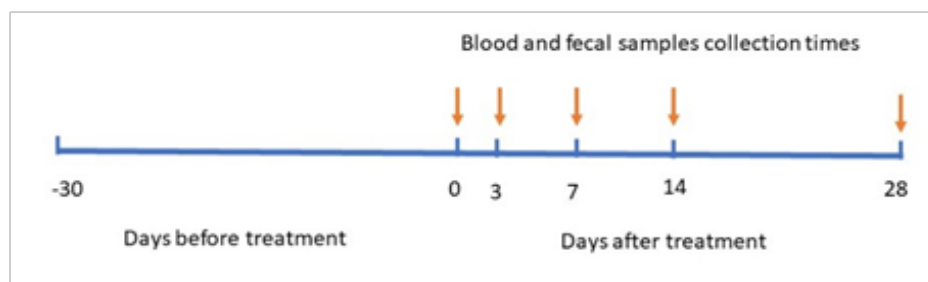


Fig. 1. Shows the experiment's design and samples collection times.

Fecal Examination

Fecal samples were individually collected from the rectum in a clean sterilized container separately. Samples were labeled and kept in the refrigerator before further analysis. The quantitative sedimentation technique was used for counting eggs of trematodes [12,13].

The egg count per gram of feces (EPG) was determined according to the following equation:

$$EPG = \frac{\text{Total number of observed eggs}}{\text{Number of chambers}} \times \frac{50 \text{ ml}/10 \text{ g}}{0.15 \text{ ml}}$$

Meanwhile, the quantitative flotation test was applied for counting eggs of nematodes [14].

Evaluation of Drug Efficacy

The anthelmintic efficiency of the used drug was evaluated by measuring egg shedding [15]. Drug efficacy was estimated by the reduction of mean in egg excretion by fecal egg count reduction test (FECRT) according to the following equation [16].

Efficacy=

$$\frac{\text{Eggs number pretreatment} - \text{eggs number post treatment}}{\text{Eggs number pretreatment}} \times 100$$

Hematological Parameters Measurement

The haematological indices were measured using an automated haematology analyzer (Prokan PE6100, China) in accordance with the manufacturer's instructions. This included haemoglobin (Hb), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular Hb (MCH), mean corpuscular Hb concentration (MCHC), red blood cells (RBCs) and total white blood cells (WBCs).

Biochemical Parameters Measurement

In the serum samples, the aspartate aminotransferase (AST) and alanine

aminotransferase (ALT) activities were measured calorimetrically [17]. Serum urea and creatinine were determined according to the previously described methods [18,19], respectively according to the manufacture kit (Spain react Co., Egypt).

Spectrophotometric Analysis of Glutathione-S-Transferase (GST)

The GST levels were measured by (Ranbut; Randox Laboratories, Antrion, United Kingdom) assay kit. GST activity was reflecting the intensities of conjugation between dinitrobenzene (CDNB) and reduced glutathione. GST can catalyze the binding of reduced glutathione (GSH) to dinitrobenzene (CDNB) and the product has an absorption peak at 340 nm [20].

Spectrophotometric Analysis of Total Antioxidant Capacity (TAC)

The (Ranbut; Randox Laboratories, Antrion, United Kingdom) was used for determining the TAC assay. The ferric reducing ability of plasma (FRAP) assay is based on the idea that antioxidants in a sample at low pH which reduce ferric-tripyridyltriazine complex to ferrous tripyridyltriazine. The final product is blue in color with a maximum absorbance at 593 nm, and the variation in absorbance is related to the sample's antioxidant ability [21].

Statistical Analyses

Data were statistically analyzed by using SPSS 25 software. The T- Self pairing test was used to explore the significant differences within growth performance data. While ANOVA with repeated measures was used for analysis the significant differences of fecal egg count, haemato-biochemical and serum antioxidant parameters data. Differences were considered significant for $p < 0.05$. The data were uniformly distributed according to the Kolmogorov Smirnov's Normality Test and were expressed as the mean \pm SEM (standard error of the mean).

Results

Anthelmintic Efficacy

The results of the anthelmintic efficacy of the tested product on different internal parasites showed that, this combination has a high efficacy against *Fasciola gigantica*, *Paramphistomum microbothrium*, and *Trichostrongylidae spp. nematodes*. A significant reduction ($P < 0.05$) in egg count has been recorded from the third day to the 7th day post-treatment in comparison with pretreatment samples. Little or no eggs have been recorded from day 14th post-treatment and on day 28th post treatment with 100% anthelmintic efficacy of this combination Table (1).

Growth Performance Parameters Before and After Anthelmintic Administration

The average body weight (BW) was significantly higher a month after treatment (213.82 kg/animal) than before treatment (177.68 kg/animal). Also, the average dry matter intake was superior a month post-treatment (253.40 kg/animal) than before treatment (236.24 kg/animal). Average weight gain significantly increases a month after treatment (36.14 KG/ month/animal). It was recorded at (25.18 /KG/ month/animal) before anthelmintic application. Feed conversion ratio was improved after anthelmintic application to be (7.01) compared to (9.38) in animals before treatment. Table (2)

Haematological Parameters

The haematological parameters of calves before and after oral administration of anthelmintic product showed significant differences as shown in table (3). Total leucocytic count and red blood cell count showed a slight increase ($p < 0.05$) from the third day to the 7th day after drug

administration followed by a decrease in WBCs count on day 14, 28 post-treatment which remain within the normal value as pre-treatment value. The RBCs count was increasing till the end of the experiment. While blood mean corpuscle volume showed a significant ($p < 0.05$) decline after administration then obviously increased again on the 28th day. Moreover, there were not any significant differences in other parameters after anthelmintics administration.

Biochemical and Antioxidant Parameters

Analysis of the biochemical and antioxidant parameters of calves before and after oral administration of anthelmintic product showed some significant differences, as shown in table (4). There were no significant differences in the ALT enzyme activity across the experiment. However, a numerical not statistical significant increase in ALT level before the treatment and on day 3 to day 7 post-drug administration followed by decreasing in its activity till the end of the experiment. Meanwhile, the AST enzyme activity showed a slight increase ($p < 0.05$) from day 3 to day 7 post-drug administration followed by decreasing in its activity till the end of the experiment. On the other side, serum creatinine levels of male calves showed a significant ($p < 0.05$) decline after administration of anthelmintic combination then transiently increased on day 14. Remarkably serum urea levels showed a significant ($p < 0.05$) decline after drugs administration. Moreover, noticeably the serum antioxidant response in calves where TAC was decreased from day 7 to the end of the trial however, GST showed a slight decrease in activity after drugs administration followed by a marked rise ($p < 0.05$) in its activity on days 14 and 28.

TABLE 1. Means of fecal egg count/g of feces before and after administration of anthelmintic combination (LEV-OXY) (M±SE).

Pretreatment	n	Pretreatment	Post treatment				Efficacy
			3 rd day	7 th day	14 th day	28 th day	
<i>Fasciola gigantica</i> .	18/30	46.10 ± 6.37 ^a	22.64 ± 4.26 ^b	6.66 ± 3.56 ^c	0.00 ^d	0.00 ^d	(100%)
<i>Paramphistomum microbothrium</i> .	14/30	197.50 ± 7.16 ^a	57.48 ± 2.03 ^b	28.68 ± 1.01 ^c	0.00 ^d	0.00 ^d	(100%)
<i>Trichostrongylidae Spp.</i>	24/30	280.00 ± 2 8.78 ^a	120.00 ± 10.69 ^b	60.00 ± 5.35 ^c	0.00 ^d	0.00 ^d	(100%)

n: number of calves infected with the different types of parasites, *Means within the same row bearing different superscripts are significantly different at ($p < 0.05$).

TABLE 2. Growth performance parameters before and after administration of anthelmintic combination (LEV-OXY) (M±SE).

Growth parameters/animal	N	Initial body weight	Duration of the trial	
			During a before treatment	During a after treatment
Average body weight Kg/animal	30	152.5± 1.73	177.68 ±1.82 ^b	213.82 ±1.94 ^a
Average dry matter feed intake kg/month/animal	30		236.24 ±0.94 ^b	253.40 ±1.24 ^a
Average gain KG/ month/animal	30		25.18 ±0.22 ^b	36.14 ±0.19 ^a
Average feed conversion ratio	30		9.38 ±0.06 ^a	7.01 ± 0.03 ^b

N: number of calves under the experiment, *Means within the same column bearing different superscripts are significantly different at (p<0.05).

TABLE 3. Hematological parameters before and after administration of anthelmintic combination (LEV-OXY) (M±SE).

Time	N	Hematological parameters						
		WBCS (10 ³ /μ)	RBCS (10 ⁶ /μ)	HB (g/dl)	HCT (%)	MCV (FL)	MCH (pg.)	MCHC (g/dl)
Before treat	30	6.44±0.28 ^c	4.29±0.18 ^c	11.46±0.36 ^a	35.53±1.13 ^a	83.56±4.82 ^a	26.95±1.55 ^a	12.15±0.82 ^a
After treatment	Day 3	7.64±0.18 ^a	4.48±0.17 ^c	11.28±0.64 ^a	34.51±1.70 ^a	69.56±2.43 ^b	22.44±0.78 ^a	14.46±0.51 ^a
	Day 7	7.62±0.36 ^a	4.65±0.18 ^b	11.61±0.41 ^a	34.98±1.98 ^a	70.54±3.66 ^b	22.75±1.18 ^a	14.37±0.79 ^a
	Day14	6.93±0.33 ^b	4.95±0.09 ^a	11.87±0.51 ^a	36.84±1.58 ^a	67.48±1.87 ^b	24.56±2.25 ^a	13.61±1.07 ^a
	Day28	6.72±0.16 ^c	5.23±0.07 ^a	11.83±0.40 ^a	36.68±1.23 ^a	82.59±2.79 ^a	26.63±0.90 ^a	12.17±0.40 ^a

(M±SE, n=30). HCT (hematocrit), MCV (mean corpuscle volume), MCH (mean corpuscle hemoglobin) and MCHC (mean corpuscle hemoglobin concentration). *Means within the same column bearing different superscripts are significantly different at (p<0.05).

TABLE 4. Biochemical and antioxidant parameters before and after administration of anthelmintic combination (LEV-OXY) (M±SE).

Time	N	Hepatorenal and antioxidant markers					
		ALT (U/ml)	AST (U/ml)	Creatinine (mg/dl)	urea (g/dl)	TAC (mM/L)	GST (U/L)
Before treat	30	17.77±1.23 ^a	0.57±0.21 ^c	0.76±0.10 ^b	20.05±1.01 ^a	0.63 ± 0.02 ^a	807.28 ± 6.42 ^a
After treatment	Day 3	18.22±1.52 ^a	1.67±0.32 ^a	0.77±0.02 ^b	13.64±0.81 ^b	0.61 ± 0.01 ^a	798.04 ± 9.69 ^b
	Day 7	19.06±1.62 ^a	1.17±0.26 ^a	0.79±0.02 ^b	12.88±0.76 ^b	0.52 ± 0.04 ^b	775.68 ±11.43 ^b
	Day14	14.77±1.33 ^a	1.00±0.28 ^b	0.89±0.04 ^a	13.72±0.98 ^b	0.52 ± 0.03 ^b	803.70 ± 6.58 ^a
	Day28	15.79±2.14 ^a	0.92±0.32 ^b	0.69±0.02 ^b	13.82±1.15 ^b	0.56 ± 0.03 ^b	813.60 ± 8.38 ^a

(M±SE, n=30). ALT (alanine aminotransferase), AST (aspartate aminotransferase), TAC (total antioxidant capacity) and GST (glutathione-S-transferase). *Means within the same column bearing different superscripts are significantly different at (p<0.05).

Discussion

Infection of farm animals raised for fattening or milk production remains a major impediment to the effective management of cattle especially because they are susceptible hosts to a high number of parasitic diseases, which result in severe economic losses to the livestock industry like obstruction of host vital organs, anemia, gastroenteritis, diarrhea, and poor weight gain [22,23]. In many countries the production system depends mainly on small-scale farms which are less developed and suffer from parasitic infection because of the ingesting of contaminated grasses and water, adding to the climatic conditions favoring the transmission [24].

Controlling this major field problem requires using a combination of active principles that have different mechanisms of action as a synergistic effect. Also, the combination of active principles plays a significant role in diminishing the development of anthelmintic resistance adding to the advantages of convenience and ease of administration [25].

The obtained results of using Levanide® oral suspension on the different internal parasites showed that this combination has a high efficacy against *Fasciola gigantica*, *Paramphistomum microbothrium*, and *Trichostrongylidae spp.* This enormous efficacy may be due to the different mechanisms of action of the two active ingredients of the tested product. The 100% efficacy of such combination against *Fasciola Sp.* in cattle under Egyptian conditions was previously recorded [26]. Moreover, another study used OXY as a flukicide with a revealed efficiency of 96% [27]. Also, using OXY alone showed a 100% reduction in the fecal egg count 14 days post-treatment [15]. On the other side, different studies recorded lower efficacy of such drugs on bovine internal parasites [28,29].

By comparing growth performance parameters during a period of one month before and one month after anthelmintic administration. Our results revealed significant improvements in daily and therefore monthly feed intake, BW, BWG, and FCR post-treatment. This improvement was mainly due to the elimination of the internal parasites. Moreover, such improvement in general

conditions and growth parameters was confirmed by the hematological results, where RBCs count showed a significant increase on the days 14th and 28th post-treatment compared to the 0, 3rd, and 7th day post-treatment with non-significant increase of hemoglobin concentration which collectively reflected the onset of good health conditions after treatment. Similar hematological findings were previously obtained as the hemoglobin, total erythrocyte count, packed cell volume, and total proteins were significantly elevated after treatment in natural infection of *Fasciola sp.* with levamisole-oxyclozanide compared to their levels before the treatment in goats [30].

Internal helminthic's infection results in the release of reactive oxygen which results in the destruction of the cell wall and hepatic tissue cirrhosis [31]. These alterations influence serum biochemical parameters. In the normal physiological state, levels of the enzymes in cells or serum are retained by regular synthesis, simultaneous degradation, inactivation, and elimination of enzymes [32]. However, due to damage to hepatic cells, the resulting enzymes are released into the blood serum and their concentration fluctuates from the physiological values [33].

Regarding the obtained biochemical results, the most pronounced parameter was the serum AST level which showed a significant increase on the third and 7th day post-treatment compared to the pretreatment level. This increase might be due to the metabolic pathway of these drugs or parasitic death and metabolic elimination of parasitic end products. Such an increase was temporary and reversible. Meanwhile, on days 14th and 28th post-treatment, serum AST levels begin to decrease which indicates a degree of hepatic tissue repair. These results agree with results of Shrimali *et al.* [30], who concluded that serum AST level initially increased then finally decreased after treatment of a natural infection of *Fasciola sp.* with levamisole-oxyclozanide compared to their levels before the treatment in goats.

Conclusion

The results of the presented study confirmed that, administration of the anthelmintic combination LEV-OXY active principals as

Levanide® Oral Suspension is a successive, efficient and safe anthelmintic against *Fasciola gigantica*, *Paramphistomum microbothrium*, and *Trichostrongylidae spp.* The growth parameters including; BW, body weight gain (BWG), feed intake (FI), feed conversion ratio (FCR), and red blood corpuscles count (RBCs) were significantly improved with minimal side effects on hematological indices, biochemical, hepatorenal and, antioxidant markers. Accordingly, it could help in increasing growth performance.

Conflict of Interest

The authors declare that there is no conflict of interests.

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Funding statement (Source)

The authors declare that the present study has no financial issues to disclose.

Authors contributions

All authors contributed to the study's conception, experiment design, and data collection, H. S. Ibrahiem: O. M. Abas, and E. B. Ata shared in examination of animals, administration of the drug, collection of samples. H. S. Ibrahiem, and A. A. Alsenosy participated in hematopathology, biochemistry, pharmacodynamic effects, and serum antioxidants analysis. E. M. El-Ktany was responsible for growth performance methodology and evaluation adding to the statistical analysis. E. B. Ata, and O. M. Abas shared in fecal samples examination and evaluation of the drug's anthelmintic efficacy. All authors commented on previous versions of the manuscript and approved the final manuscript.

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List of abbreviations

Abbreviation	Full name	Abbreviation	Full name
ALT	Alanine aminotransferase	GST	Glutathione-S-transferase
ANOVA	Analysis of variance	HB	Haemoglobin
AST	Aspartate aminotransferase	HCT	Hematocrit
BW	Body weight	LEV	Levamisole
BWG	Body weight gain	MCH	Mean corpuscular haemoglobin
CDNB	Dinitrobenzene	MCHC	Mean corpuscular haemoglobin concentration
EPG	Egg count per gram	MCV	Mean corpuscular volume
FCR	Feed conversion ratio	OXY	Oxyclozanide
FECRT	Fecal egg count reduction test	RBCs	Red Blood Corpuscles count
FI	Feed intake	TAC	Total antioxidant capacity
FRAP	Ferric reducing ability of plasma	WBCs	Total white blood cells

التأثيرات الطارد للديدان والتأثيرات الديناميكية الدوائية لمزيج الليفاميزول-أوكسيكلوزانيد (الليفانيد)[®] في عجول التسمين

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ثلاثون عجلا بمتوسط أعمار سنة واحدة ووزن جسم حوالي 152.5 كجم تم فحصها للتأكد من وجود عدوى مختلطة من الطفيليات الداخلية المختلفة مثل ديدان الفاشيولا، بارامفيستوموم ميكروبوثيريوم، و تريكوسترونجيليديا. واستخدمت هذه العجول لتقييم التأثير الطارد للديدان، ومعدلات أداء النمو ومعايير الكيمياء الحيوية ومضادات الأكسدة في الدم الناتج من تناول جرعة واحدة عن طريق الفم من عقار (الليفانيد)[®] والذي يحتوي علي (ليفاميزول و أوكسيكلوزانيد) كمواد فعالة بجرعة 2.5 مل من المنتج لكل 10 كجم من وزن الحيوان. أظهر اختبار خفض عدد البيض البرازي للحيوانات التي تم اختبارها انخفاضا كبيرا ($p < 0.05$) في عدد البويضات لكل غرام من البراز للطفيليات التي تم فحصها بداية من اليوم الثالث ثم في اليوم السابع بعد بدء العلاج بالمقارنة مع العينات قبل بدء العلاج بنسبة فعالية 100% كطارد للديدان. إضافة إلي وجود تحسن في معدلات أداء النمو وعدد كرات الدم الحمراء تحسنا ملحوظا فيما بعد العلاج. وقد لوحظ ارتفاع عكسي طفيف في مستوى انزيم أمينوترانسفيراز في اليوم الثالث إلى اليوم السابع بعد تلقي العلاج تبعه انخفاض في نشاطه حتى نهاية التجربة. كما انخفض إجمالي قدرة مضادات الأكسدة بداية من اليوم السابع؛ وأظهرت النتائج انخفاض مستوي انزيم الجلوتاثيون-س-ترانسفيراز انخفاضا طفيفا بعد تجريب الدواء وتلاه إرتفاع ملحوظ ($p < 0.05$) في يومي الرابع عشر والثامن والعشرين بعد تجريب الدواء. وبناء على ذلك، يمكن استنتاج أن مزيج الليفاميزول-أوكسيكلوزانيد يمكن أن يستخدم كطارد للديدان بفعالية وأمان كما يمكن أن يساعد في زيادة معدلات أداء النمو.

الكلمات الدالة: (ليفاميزول-أوكسيكلوزانيد)، طارد للديدان، أداء النمو، كيمياء الدم الحيوية.