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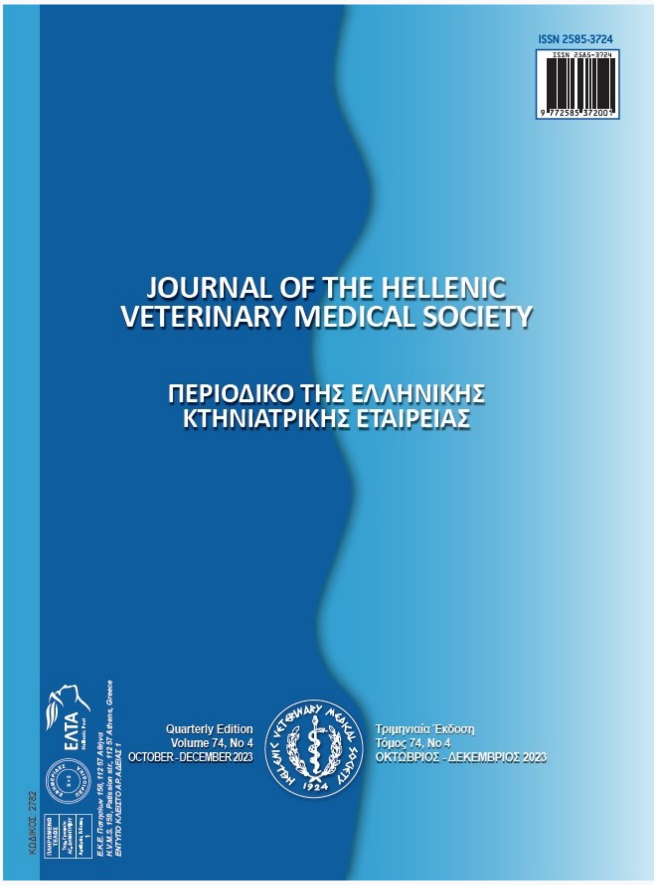


# The efficacy of Contoya (Lobelia decurrens cav.) in the control of eimeriosis in vivo in rabbits

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**Research article**
**Ερευνητικό άρθρο**

# The efficacy of Contoya (*Lobelia decurrens*Cav.) in the management of intestinal coccidiosis in rabbits

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**ABSTRACT:** The pursuit of alternatives for coccidiosis management, combined with the dearth of studies on local bioactive plants, prompted the current study to assess the efficacy of Contoya (Lobelia decurrens Cav.) in two distinct forms for controlling Eimeria spp. in rabbits in Cajamarca, Peru. Fifty-six rabbits exhibiting a parasite burden exceeding 400 oocysts per gram of feces were selected and divided into a control group and six treatment groups, each consisting of eight individuals. The initial three treatment groups received Contoya in an extract form, while the subsequent three received it as an infusion. Coproparasitological evaluation was conducted using McMaster's technique on days one, three, and eight post-administration. The outcomes demonstrated that both forms and dosages of Contoya achieved a reduction in parasite load, thereby validating the applicability of this plant in extract and infusion forms, ranging from one to three milliliters per rabbit, regardless of weight. The effectiveness of Contoya over the studied days exhibited significance ($p<0.05$). The Contoya extract treatments showcased a maximal reduction of 99.04% (Day 1) and a minimum efficacy of 89.35% (Day 8). Similarly, in the group treated with Contoya infusion, the utmost reduction of oocysts was attained (99.62% - Day 1); however, this group also recorded the lowest value (84.96% - Day 8). In conclusion, Contoya (Lobelia decurrens Cav.) effectively manages coccidiosis in rabbits, in both extract and infusion presentations.

***Keywords:*** antiparasitic; efficacy; coccidiosis; parasite load; *Lobelia decurrens* Cav.

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## INTRODUCTION

Coccidiosis stands as one of the most prevalent parasitic afflictions among rabbits, predominantly impacting juveniles, while adults commonly function as carriers through the excretion of oocysts into the environment. These oocysts subsequently contaminate other rabbits through the consumption of sporulated oocysts present in food or water (Duszynski and Couch, 2013). The intensity of the ailment hinges on various factors, including the number of infectious oocysts ingested, the specific coccidia species implicated, their favored habitat, and cellular affinity within the rabbit host. Furthermore, the individual immune and nutritional status of each rabbit plays a pivotal role in the disease's severity (Hanada et al., 2003; Duszynski and Couch, 2013).

Clinical manifestations of coccidiosis in rabbits can encompass a coarse fur appearance, diminished sheen, despondency, reduced appetite, compromised feed conversion, abdominal discomfort, distension, dehydration, reduction in weight, pallid and moist mucous membranes, and, notably, diarrhea that may be abundant, occurring within a span of 4 to 6 days following infection. In severe instances, mortality can also occur (Hanada et al., 2003; Jing et al., 2016).

In the pharmacological management of this parasitic condition, toltrazuril has predominantly been employed. Other antiparasitic agents, such as sodium sulfadimidine and amprolium, have also been utilized. However, research has indicated a decline in the effectiveness of these three drugs in controlling coccidiosis among rabbits (Qamar et al., 2013). Trimethoprim-sulfamethoxazole and amprolium hydrochloride have also demonstrated ineffectiveness in controlling clinical coccidiosis in rabbits (Ogolla et al., 2018). As a result, the pursuit of alternative treatment approaches becomes crucial to prevent the proliferation of anticoccidial resistance. Notably, bioactive plants have shown promising results in controlling various animal parasites (Silva et al., 2014; Sharma et al., 2021).

In scenarios marked by elevated parasite levels and the prevalence of antiparasitic resistance, it becomes imperative to explore and incorporate alternative control measures. This entails leveraging a multitude of strategies to curtail reliance on pharmaceutical interventions and enhance animal production efficiency (Burke and Miller, 2020).

Plant-derived preparations have historically been employed in therapeutic approaches for disease management, encompassing parasitic control, in both human and livestock contexts (Silva et al., 2014; Ranasinghe et al., 2023). Furthermore, their utilization offers advantages such as cost-effectiveness and prompt outcomes (Appendino et al., 2014). Additionally, these preparations exhibit lower toxicity when contrasted with pharmaceutical compounds utilized in therapeutic applications.

Cajamarca is a region with ideal conditions for rabbit farming. Within the region, there is a practice of both family and commercial breeding, aimed at human consumption due to its high protein content, as well as for pet ownership. Rabbit meat contains nutrients of significant biological value, which could potentially reduce the percentage of child malnutrition in the region, given that Cajamarca is one of the Peruvian regions with the highest rates of child malnutrition (IPE, 2022).

Contoya (*Lobelia decurrens*) is a plant native to the Andes that has not received the necessary attention from Peruvians. There are very few reports providing information about this plant. In a previously documented study, the activity of *Lobelia decurrens* Cav. was evaluated against *Fasciola hepatica* in guinea pigs, demonstrating fasciolicidal activity. Phytochemical analysis of the plant revealed the presence of alkaloids, flavonoids, tannins, saponins, and steroids (Sánchez, 2005). In another Chinese study, a different member of the same *Lobelia* family, *L. chinensis* Lour, exhibited anti-*Mycobacterium tuberculosis* activity in extract form (Choi and Lee, 2016).

In this context, the primary aim of this investigation was to assess the effectiveness of Contoya (*Lobelia decurrens* Cav.) in two distinct formulations for managing *Eimeria* spp. in rabbits (*Oryctolagus cuniculus*). Furthermore, this study aimed to explore the prospective applicability of Contoya in forthcoming research involving other domestic species. Notably, the plant's cultivation is indigenous to specific provinces within the Cajamarca region, in Peru.

## MATERIAL AND METHODS

### Place

The investigation was conducted at the Instituto Nacional de Investigación Agraria - INIA, Estación experimental Los Baños del Inca (Cajamarca), in collaboration with the Laboratorio de Parasitología Veterinaria y Enfermedades Parasitarias of the Universidad Nacional de Cajamarca.The INIA is situated at an altitude of 2665 meters above sea level. It experiences a dry temperate climate with an average annual temperature of 15.2 °C.

The rabbits were animals bred at the INIA as part of their farm animal breeding and improvement program. These rabbits were fed a diet consisting of green forage (*Lolium multiflorum*and *Medicago sativa*) and concentrated feed. They were housed in groups of three to four individuals in wooden cages with walls made of metal mesh. The majority of rabbits exhibited rough fur, were depressed, and in some cases, showed signs of diarrhea.

**Pre-dosage and sample analysis**

Using the McMaster technique modified by Gordon & Whitlock (Ueno and Gonçalves, 1998), an initial exhaustive sampling of 100 rabbits was carried out. From the results of the analyses, *Eimeria* spp. was identified (Figure 1). From this initial cohort, a subset of 56 animals of the fawn Burgundy and California breeds, older than three months of age and harboring a parasite load greater than 400 OPG (oocysts per gram of feces), naturally infected, was meticulously selected. Subsequently, this selected group was segregated into distinct entities: a control group and six treatment groups, each consisting of eight individuals.

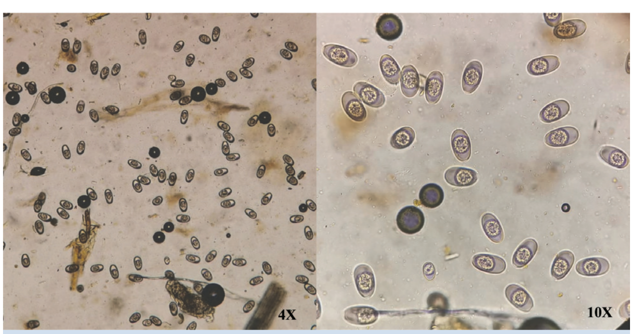


**Figure 1.** *Eimeria* spp. oocysts found in fecal samples from the rabbits.

For the McMaster technique, 3 g of feces were weighed, homogenized in 42 mL of oversaturated sugar solution, and then filtered through a tea strainer. Using a Pasteur pipette, a small quantity of the solution was withdrawn to fill both areas (0.3 mL) of the McMaster slide (0.15 mL per area). The mixture was allowed to settle for 5 minutes and subsequently observed under a microscope using a 10X eyepiece and a 10X objective lens. Both areas of the slide were counted from left to right, and the total observed oocysts were multiplied by 50 to calculate the OPG.

***Lobelia decurrens*Cav. plant and solutions**

The botanical specimen was meticulously collected in its entirety, encompassing the root, stem, leaves, and flowers, from the village of El Carrizo within the district and province of San Pablo (Figure 2). Subsequently, *Lobelia decurrens* Cav. underwent processing via two distinct methodologies: extract and infusion.

**Figure 2.** *Lobelia decurrens* Cav. plant in its natural habitat.

Extract: to obtain the extract, 250 g of the fresh plant material (including roots, stems, leaves, and flowers) was utilized and blended using an electric blender with 500 mL of cold-boiled water. The resulting solution was filtered through a metal mesh strainer into a beaker, thus achieving the extract.

Infusion: to prepare the infusion, the entire plant (roots, stems, leaves, and flowers) was first sun-dried and subsequently pulverized in a mortar. Following this, 250 g of powdered Contoya was weighed and added to 500 mL of boiling water (90 °C) in a metal container. Lastly, the mixture was allowed to cool, and it was filtered through a mesh sieve, resulting in the Contoya infusion.

**Administration of *Lobelia decurrens*Cav.**

The Contoya extract and the infusion were administered individually to the rabbits in both groups using a 10 mL syringe, with the necessary care to avoid any harm or stress to the rabbits. Each solution was agitated beforehand, and the administration was carried out orally. Under the presentation, volume, and distribution, the protocol shown in Figure 3 was followed.

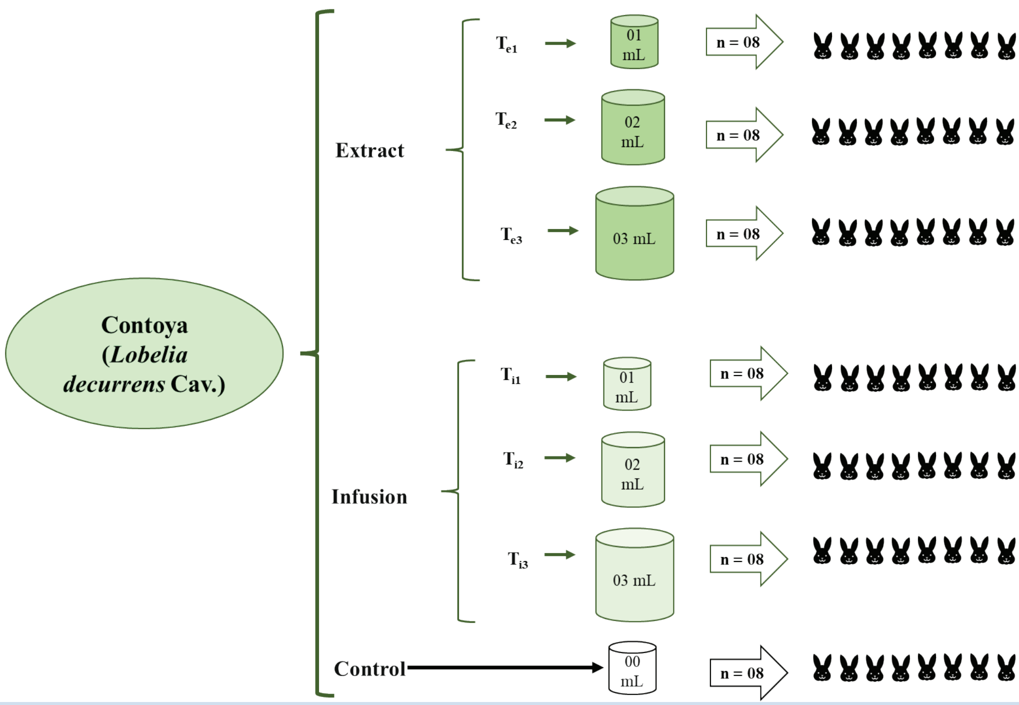


**Figure 3.** Administration and dosage of Contoyaextract and infusion in the treatment groups

**Table 1.** Phytochemical composition of *Lobelia decurrens* Cav.

| Part | Extract | Analytical technique and constituents | |
|---|---|---|---|
| Flower | Methanolic | Shinoda + (F) | NaOH 10% + (S, F) |
| | | (HCl qp) + | |
| | | Gelatin + (T) | ($FeCl_3$) + |
| | | Dragendorff + (F, A) | Mayer + (F) |
| | Dichloromethane | Liebermann B + (S, Q) | |
| | Aqueous | Gelatin + (T) | |
| | Acid | Dragendorff + (A) | Mayer + (A) |
| Leave | Methanolic | Dragendorff + (F) | Liebermann B + (T) |
| | | (FeCl3) + (F) | Mayer + (S, F) |
| | Dichloromethane | Mayer + (E, Q) | |
| | Aqueous | Foam + (Sa) | Liebermann B + (T) |
| | Acid | ($FeCl_3$) + (A) | Dragendorff + (A) |
| Stem | Methanolic | Mayer + (S, F) | Liebermann B + (T) |
| | Dichloromethane | Mayer + (E, Q) | |
| | Aqueous | Liebermann B + (T) | |
| | Acid | Dragendorff + (A) | |
| | | ($FeCl_3$) + (A) | |
| Root | Methanolic | ($FeCl_3$) + (F) | |
| | Aqueous | Foam + (Sa) | Liebermann B + (T) |
| | Acid | Dragendorff + (A) | |
| | | ($FeCl_3$) + (A) | |

Flavonoids (F), Steroids (S), Alkaloids (A), Tannins (T), Quinones (Q), Saponin (S)

**Analysis of the phytochemical composition of *Lobelia decurrens* Cav.**

The chemical composition analysis was conducted using the Photochemical March of the Drop Test at the Laboratorio de Farmacología de la Facultad de Farmacia y Bioquímica, Universidad Nacional de Trujillo. The outcomes of the phytochemical assessment of the *Lobelia decurrens* Cav. plant are detailed in Table 1.

### Post-treatment collection of fecal samples

The rabbits were kept in clean individual cages from which the feces expelled during the nights were collected the following day (50 g) in polyethylene bags and transferred to the laboratory for coproparasitological analysis using the McMaster method modified by Gordon and Whitlock, for the quantification of OPG. These actions were performed on the first, third, and eighth day in the morning hours (9 hours).

### Contoya efficacy

The anticoccidial efficacy of Contoya was calculated based on the percentage reduction of OPG using the following formula (Wood et al., 1995):

$$\%\text{Efficacy}=\frac{\text{Mean OPG Control group-Mean OPG (Post-treatment)}}{\text{Mean OPG Control group}}\times 100$$

### Statistical analysis

The statistical analyses were performed utilizing IBM SPSS Statistics 25.0. The reduction in OPG was computed, and an Analysis of Variance (ANOVA) was conducted, wherein the assessed variables were the count of oocysts to time. Additionally, a 95% confidence interval for the percentage reduction of oocysts (efficacy) was calculated.

### Ethical statements

All procedures undertaken in this study were executed in strict adherence to the legal guidelines stipulated by the Peruvian State's Ley de Protección y Bienestar Animal (Ley N° 30407) as well as the ethical regulations established by the European Directive 2010/63/EU concerning the utilization of animals in scientific research.

## RESULTS

After the second post-treatment day, the initially observed clinical signs (rough fur, lethargy, and diarrhea) gradually started to subside. The oocysts per gram of feces (OPG) of *Eimeria* spp. decreased after the administration of Contoya (Table 2).

The positive rabbits and oocysts per gram of feces significantly decreased from Day 0 to Day 1 ($p<0.05$), after which the number of positive rabbits started to increase (Table 3, Figure 4).

Through the assessment of oocyst counts per gram of feces of *Eimeria* spp., the efficacy of Contoya was higher on Day 1 and gradually decreased by Day 8 in both the groups of rabbits treated with Contoya extract and infusion (Table 4).

**Table2.** Comparative effect of different *Lobelia decurrens* Cav. presentations as expressed by the average OPG of *Eimeria* spp.

| Presentation | Treatments | OPG ($\bar{x}$) | | | |
|---|---|---|---|---|---|
| | | Pre-dosage | Post-dosage | | |
| | | Day 0 | Day 1 | Day 3 | Day 8 |
| | Control | 1531.5 | 1481.25 | 1512.5 | 1506.25 |
| **Extract** | $T_{e1}$ | 412.5 | 25 | 31.25 | 131.25 |
| | $T_{e2}$ | 425 | 12.5 | 68.75 | 162.5 |
| | $T_{e3}$ | 1150 | 18.75 | 18.75 | 56.25 |
| **Infusion** | $T_{i1}$ | 1178.75 | 18.75 | 18.75 | 168.75 |
| | $T_{i2}$ | 3687.5 | 25 | 43.75 | 137.5 |
| | $T_{i3}$ | 3775 | 43.75 | 68.75 | 200 |

**Table 3.** Comparative effect of different *Lobelia decurrens* Cav. presentations on positive rabbits and OPG of *Eimeria* spp.

| Time | Presentation | | | |
|---|---|---|---|---|
| Days | Extract | | Infusion | |
| | Positives (%) | OPG | Positives (%) | OPG |
| 0 | 100.00$^{a}$ | 3687.5$^{y}$ | 100.00$^{a}$ | 3778.00$^{y}$ |
| 1 | 37.50$^{c}$ | 25.00$^{z}$ | 50.00$^{c}$ | 43.75$^{z}$ |
| 3 | 62.50$^{bc}$ | 43.75$^{z}$ | 62.50$^{bc}$ | 68.75$^{z}$ |
| 8 | 75.00$^{ab}$ | 137.50$^{z}$ | 75.00$^{ab}$ | 200.00$^{z}$ |
| **Average** | **68.75$^{a}$** | **973.44$^{y}$** | **71.88$^{a}$** | **1021.9$^{y}$** |

$^{a,b,c,y,z}$ Different letters within the same row and column of the same variable indicate a statistical difference ($p<0.05$).

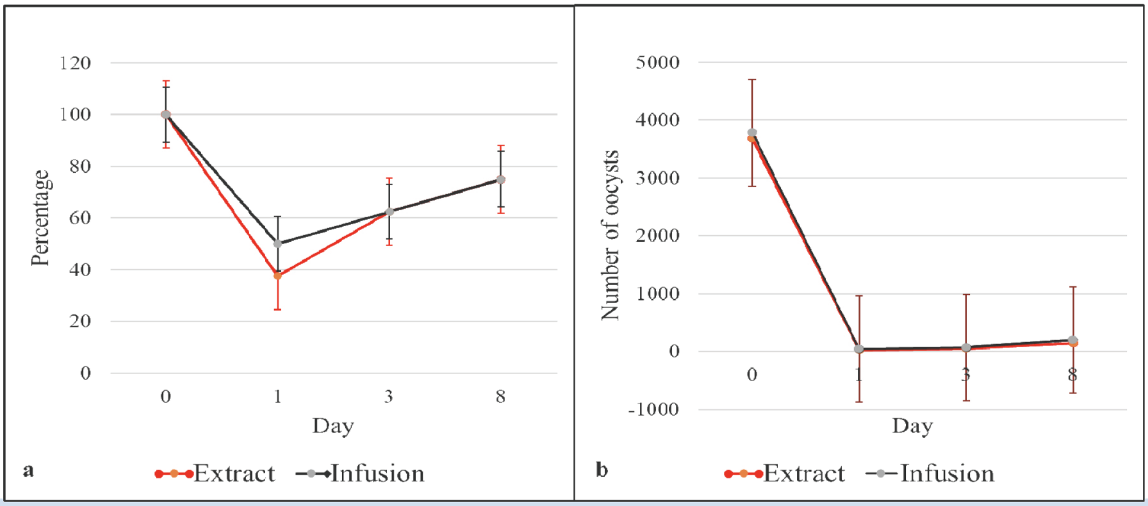


**Figure 4.** Effect of *Lobelia decurrens* Cav .among treatments based on positive animals (a) and oocysts counts (b).

**Table 4.** Efficacy of Contoya based on reduction of *Eimeria* spp. oocysts.

| Presentation | Treatments | Percentage of oocyst reduction (% Efficacy) | | |
|---|---|---|---|---|
| | | Day 1: % (95% CI) | Day 3: % (95% CI) | Day 8: % (95% CI) |
| | $T_{e1}$ | 98.43 (97.82 - 99.04) | 97.95 (97.24 - 98.66) | 91.27 (89.84 - 92.70) |
| **Extract** | $T_{e2}$ | 98.43 (97.82 - 99.04) | 98.74 (98.18 - 99.30) | 96.27 (95.31 - 97-23) |
| | $T_{e3}$ | 98.43 (97.82 - 99.04) | 97.09 (96.24 - 97.94) | 90.81 (89.35 - 92.27) |
| | $T_{i1}$ | 99.18 (98.74 - 99.62) | 96.70 (95.80 - 97.60) | 89.14 (87.57 - 90.71) |
| **Infusion** | $T_{i2}$ | 97.23 (96.42 - 98.04) | 98.74 (98.18 - 99.30) | 88.74 (87.14 - 90.34) |
| | $T_{i3}$ | 97.23 (96.42 - 98.04) | 95.44 (94.39 - 96.49) | 86.68 (84.96 - 88.40) |

CI: Confidence Interval

## DISCUSION

Both the Contoya extract and infusion decreased the number of positive rabbits and the oocysts per gram of feces of *Eimeria* spp., which could be attributed to the bioactive components of the Contoya plant. Flavonoids, alkaloids, and saponins are among the main phytochemical components detected in *Lobelia decurrens* Cav., similar to those described in the *Lobelia* genus, along with other constituents (Sánchez, 2005; Stolom et al., 2016; Wang et al., 2018).

Phenolic and flavonoid compounds play a role in plant protection against both abiotic and biotic factors (Ohri and Pannu, 2010). These components, along with limonoid alkaloids, quassinoids, saponins, and essential oils, have demonstrated significant suppression of egg hatching and nematotoxic activity (Mwamula et al., 2022). Similarly, flavonoids have exhibited efficacy against several common protozoa in humans, including *Entamoeba, Giardia, Trichomonas*, and others (Ramírez et al., 2010).

Tannins exert a similar action to phenols by inhibiting enzymes involved in cellular respiration, resulting in the suppression of oxidative phosphorylation and respiration (Ohri and Pannu, 2010). Moreover, saponins possess the capability to bind to free proteins within the animal's gastrointestinal tract or glycoproteins in the nematode's cuticle, thereby triggering their mortality (Mali and Wadekar, 2008). Similarly, it is plausible that Contoya acts on *Eimeria* spp. in rabbits, given that these parasites reside within the intestinal epithelial cells, leading to their demise and the inhibition of oocyst reproduction. On another note, saponins exert their biological action through specific interactions with the cell membrane, facilitating cellular permeability (Zheng and Gallot, 2020). Meanwhile, alkaloids are neurotoxic compounds that disrupt neurotransmitter release (Luo et al., 2018).

In addition to the observed effectiveness of *Lobelia decurrens*Cav. in controlling coccidiosis in rabbits, this plant is considered safe. The reported LD50 is ≥ 5000 mg/kg, indicating that it is not a toxic plant (Stolom et al., 2016). When comparing the positive cases between the Extract and Infusion treatments and the administered volumes, no statistical difference was identified ($p$>0.05), suggesting that both presentations and doses ranging from 1 to 3 mL per rabbit can be utilized.

It is conceivable that *Lobelia decurrens* Cav. may exhibit a short residual effect within the organism due to the lack of purification of its active principle. This is evident as it achieved a remarkable efficacy of up to 99.62% on Day 1 ($T_{i1}$), which subsequently declined to the lowest value of 84.96% by Day 8 ($T_{i3}$). The latter value, along with others below 95% and the lower limits of the 95% confidence interval below 90%, raises concerns about resistance or suspected resistance. According to the World Association for the Advancement of Veterinary Parasitology, this applies in cases involving purified antiparasitic when either of the two criteria is met (Coles et al., 1992).

The efficacy obtained from both Contoya presentations was undoubtedly superior to that of sodium sulfadimidine (71%), toltrazuril (66.6%), and amprolium (60%), as reported by Qamar et al. (2013). In another study, toltrazuril achieved an efficacy of 67.6% at a single dose of 5 mg/kg and 64.6% at a dose of 2.5 mg/kg administered two times. Amprolium alone demonstrated an efficacy of 71%, while a combination of toltrazuril and amprolium exhibited an efficacy of 74% (El-Ghoneimy and El-Shahawy, 2017). Other active ingredients such as sulfacloropyrazine and diclazuril have been effective against clinical coccidiosis in rabbits, unlike trimethoprim-sulfamethoxazole and amprolium hydrochloride, which have not shown efficacy (Ogolla et al., 2018).

Even though the efficacies of the aforementioned anticoccidials did not reach 100%, they did lead to a reduction in OPG and the mortalities associated with coccidiosis in rabbits. Moreover, rabbits exhibited improved productivity parameters. Antiparasitic treatments with efficacies below 90-95% can still hold significant value, as they substantially reduce the parasite load, thus preventing severe harm to animal health and productivity (Forbes, 2013). Additionally, when employing bioactive plants, the process tends to be less costly, rendering it a more feasible and sustainable option. This approach also avoids the presence of toxic residues in products and by-products originating from animals (Appendino et al., 2014).

Hence, the utilization of plants possessing antiparasitic activity can serve as a valuable strategy to diminish reliance on conventional pharmacological drugs. The diverse array of phytochemical components like flavonoids, phenols, tannins, saponins, and terpenes, among others, have exhibited efficacy against a wide spectrum of parasites (Anthony et al., 2005). This approach enables the adoption of integrated and sustainable approaches for parasitosis control.

## CONCLUSION

The observed effect in the reduction of *Eimeria* spp. in rabbits could potentially be attributed to the synergistic interaction among Contoya's (*Lobelia decurrens* Cav.) components, including flavonoids, steroids, alkaloids, tannins, quinones, and saponins. Contoya proves effective in treating coccidiosis in rabbits, and it can be used interchangeably in both extract and infusion forms at a volume of one to three mL per animal. The liquid extract presentation is the simplest to prepare, making it a more practical option.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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