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Anthelmintic activity of *Cratyliamollis* leaves against gastrointestinal nematodes in goats

Atividade anti-helmíntica de folhas de "Cratyliamollis" contra nematóides gastrintestinais de caprinos

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SUMMARY

The present study assessed the *in vivo* anthelmintic activity of the *C. mollis* leaf decoction extract when administered orally to naturally infected goats with gastrointestinal nematodes. To this, animals were randomized into three groups:non-treated, control (treated with doramectin 1mL/50 kg b.w.) and *C. mollis* extract treated groups (2.5mg/kg b.w.). Blood and faecal samples were collected from each animal at day 0, and 30th day post-treatment to monitor immunological and parasitological parameters. A significant faecal egg reduction (61.1%) and an increase in IgA and eosinophils levels were observed in the *C. mollis* extract treated group, in comparison to the untreated and doramectin groups. Considering that gastrointestinal nematode infections in small ruminants are serious problems in the world, causing economic losses worldwide, associated to high anthelmintic cost, resistance to available anthelmintics and residue problems in meat and milk for human consumption, the plant extract use is an area of interest to search new anthelmintic agents. Thus, *Cratyliamollis* Mart. Ex Benth, an important medicinal plant from Brazilian Northeast semi-arid region, is used to treat different types of diseases, and as forage supplementation. Therefore, the data indicated the potential anthelmintic activity of *C. mollis* extract; further research is thereby warranted to assess its value for therapeutic purposes.

Keywords: plant extract, parasiticidal, immune response, small ruminats

RESUMO

Este estudo avaliou a capacidade anti-helmíntica *in vivo* do extrato aquoso de folhas de *C. mollis*, administrado por via oral em caprinos naturalmente infectados com nematódeos gastrintestinais. Para isto, os animais foram aleatoriamente distribuídos em três grupos (grupo não tratado, grupo controle tratado com doramectina (1mL/50 kg de peso corpóreo) e grupo tratado com o extrato aquoso de *C. mollis* (2,5mg/ kg de peso corpóreo). Amostras de sangue e fezes foram colhidas de cada animal nos dias 0 e 30 após o tratamento para verificar parâmetros imunológicos e parasitológicos. Uma redução significativa na oviposição (61,1%) e um aumento dos níveis de IgA e eosinófilos foram observados no grupo tratado com o extrato aquoso, em comparação aos grupos controle (não tratado e tratado com doramectina). Considerando que nematódeos gastrintestinais de pequenos ruminantes causam perdas econômicas ao nível mundial, devido ao custo e à resistência aos anti-helmínticos disponíveis, além do efeito residual nos derivados animais para consumo humano, os extratos vegetais apresentam-se como uma fonte alternativa de anti-helmínticos. Assim, *Cratyliamollis* Mart. ExBenth é uma planta usada no semi-áridodo Nordeste brasileiro para tratardoenças e como forragem. Portanto, os resultados indicaram o potencial anti-helmíntico do extrato, embora mais estudos sejam necessários para validar seu uso para fins terapêuticos.

Palavras-chave: extrato vegetal, parasiticida, resposta imune, pequenos ruminantes

INTRODUCTION

Gastrointestinal nematodes infections negatively affect health and the overall productivity of goats, causing economic losses worldwide (CHARLIER et al., 2015). As the anthelmintic resistance has become a global problem in these herds, due to broad-spectrum chemotherapeutic agents and their irrational use, new anthelmintic shave been introduced to the market, but the treatment of these infections remains a problem in farm animals by the occurrence of drug resistant nematodes (FORTES & MOLENTO, 2013; BÁRTÍKOVÁ et al., 2016). Thus, new strategies for parasite control are necessary (GEARY et al., 2015; Van der REE & MUTAPI, 2015).

In order to delay the evolution of this resistance, phytotherapy offers natural alternative to drug treatment, once plants are used as sources of pharmaceuticals and as traditional medicine formulations and are of value in new drug discovery, owing to its plant chemical composition (DOMINGUES et al., 2010; FONSECA et al., 2013). So, plants have been investigated and several studies have reported secondary metabolites as promising new source of with anthelmintic properties (BORGES-DOS-SANTOS et al., 2012; AHMED et al., 2014; KANOJIYA et al., 2015; SACHAN et al., 2015).

In this context is inserted *Cratyliamollis* Mart. Ex Benth (Leguminosae family), a legume shrub native from the Northeast semi-arid region of Brazil, especially in “caatinga”. This species is popularly known as “camaratuba” or “camaratu” and is highly resistant to desiccation (LIMA et al., 2009). Their leaves are widely used as forage to improve livestock nutrition (SANTOS et al., 2008) and in folk medicine, used against gastrointestinal nematodes (ALBUQUERQUE et al., 2007). Although there are some phytochemical data, this is the first report assessing the anthelmintic activity of the leaf decoction extract of *C. mollis* in goats naturally infected with gastrointestinal nematodes by parasitological and immunological procedures.

MATERIALS AND METHODS

C.mollis leaves were collected in the semi-arid region of Bahia, Brazil. A voucher herbarium specimen (number LP5119) was deposited at Herbarium of Universidade Estadual de Feira de Santana, Bahia, Brazil. Leaves were air dried in an oven at 40ºC. The powdered material (200g) was extracted with boiling water for 20min. The *C. mollis* leaf decoction extract was filtered and lyophilized for bioassay analysis.

For the antigen preparation, adults *H. contortus* of either sex were harvested from slaughtered goat abomasums, rinsed three times withice-cold PBS (140mM NaCl, 2.6mM KCl, 6.4mM Na_2HPO4, and 1.4mM KH_2PO_4, pH 7.2), prior the parasites disruption in PBS pH 7.2 at 4°C by 30s periods of sonication. The lysate was centrifuged at 1200×*g* for 15min at 4°C, and the supernatant was either used immediately or stored at -20°C for ELISA antigen test.

To evaluate the *C. mollis* extract anthelmintic effect, a study design was conducted with mixed bred goats naturally infected with gastrointestinal nematodes, randomized into three groups (n = 12 animals in each group):negative control (no treatment),positive control (doramectin, 1mL/50kg b.w., Dectomax®, Pfizer, according to the manufacturer's instructions) and *C. mollis* extract treated group (2.5mg/kg b.w.). The dose extract was established as described by Borges-dos-Santos et al. (2012).The substances were administered through three consecutive doses from the time zero.

Animals were maintained under similar management and feeding conditions at the Experimental Station of Bahia Company for Agro-Livestock Development (EBDA) in Juazeiro, Bahia, Brazil. Goats were grazing under traditional extensive management in the Brazilian semi-arid region. All animal studies were carried out according to the guidelines for the care and use of laboratory animals of the Brazilian College of Animal Experimentation (COBEA).

For assessing the extract anthelmintic effect, faecal samples were collected directly from the rectum of each animal to determine faecal egg count (FEC)at day 0 and at 30thday post-treatment. Samples were processed according to the modified protocol described by McMaster (Whitlock, 1955). Results are expressed as eggs per gram.On the other hand, blood samples were collected from each animal by puncturing the jugular vein in EDTA-coated tubes to monitor packed cell volume (PCV) and differential leukocyte count at the same periods described before. The PCV was measured by the microhaematocrit method. Sera were recovered and frozen at -20°C until analysis to monitor immunological parameters.

For serological assay, ELISA was used to detect total IgG and IgA levels. Briefly, 100µL serum samples (1:200 diluted in PBS/0.05% Tween/0.25% defatty powered milk) were added to the plate and incubated (1h/37°C). All serum samples (test, negative and positive controls) were done in triplicate. After washing, plates were sequentially incubated (1h/37°C) with anti-goat HRP conjugated IgG (100µL) (Bethyl Labs, Texas, USA) and developed by addition of 100mL of chromogenic solution (15mL of 0.1 M citrate phosphate buffer, pH 5.0 containing 6mg *o*-phenylendyamine) and 10µL of H_2O_2. After 20min of incubation, the reaction was stopped with 50µL of 0.5M H_2SO_4. Reactions were measured at 450 nm in an ELISA reader (Stat Fax®, USA).

All animals were also monitored with regard to their body weight at the same collection intervals. The monitoring was carried out between March and May, coinciding with the end of the dry season and beginning of the rainy period.

Results were expressed as means ± standard deviation (SD), using Kruskal-Wallis non-parametric (ANOVA on ranks) tests for parametric distribution and as median and confidence intervals for non-parametric data, using the statistical software Graph Pad (San Diego, USA). $P<0.05$ were considered statistically significant.

RESULTS AND DISCUSSION

This study was conducted in goats naturally infected with gastrointestinal nematodesas a preliminary assessment of anthelmintic activity to establish some parasitological, haematological and immunological changes in response

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to the *C. mollis* leaf decoction extract treatment.

Regarding haematological results, PCV values, leukocyte and haemaglobincounts during the experimental period, no statistically significant differences were observed between animals from each group (P >0.05), *i.e.*, into the three groups:non-treated, doramectin group and extract treated groups during the experimental period. However, only the eosinophils level was significantly in the infected goat group treated with extract treated group (P<0.05), compared to non-treated and doramectin control groups (Figure 1).

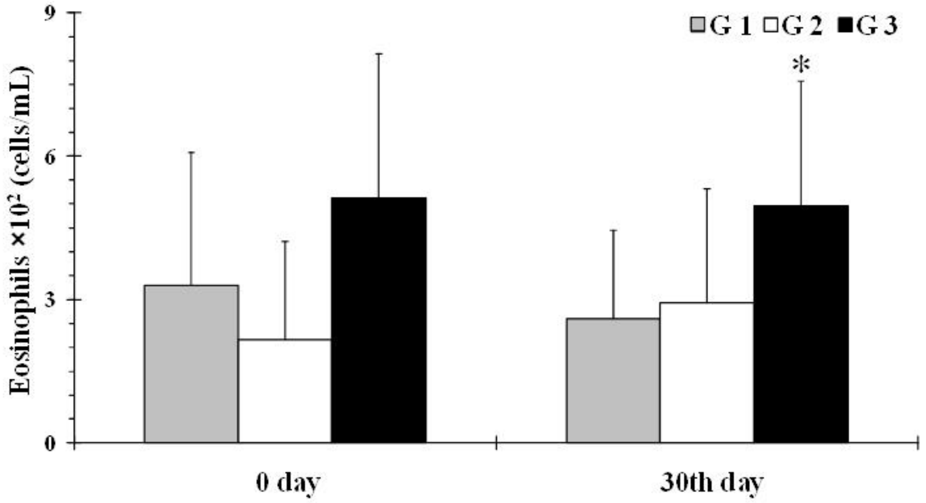

Figure 1. Bar diagrams showing the effect of *Cratyliamollis* leaf decoction extract on circulating eosinophil level in goats naturally infected with gastrointestinal nematodes. Values are means ± standard deviation. Significant differences are noted by an asterisk (P<0.05). G1: Negative control (untreated), G2: Positive control (treated with doramectin, 1mL/50 kg b.w.), G3: animals treated with 2.5mg/kgof extract

With respect to body weight examination, it was observed that the live body weight of goats treated with extract change during the experimental period, although no statistically significant differences were observed into the three groups (P >0.05). Notwithstanding, the extract treated group gained more body weight compared to negative and positive control groups (Table 1).

Concerning the *C. mollis* extract anthelmintic activity showed significant decrease in the mean faecal egg count throughout the experimental period in extract treated group compared to negative and positive controls. The average FEC reduction percentage was 61.1% (P<0.005) at 30th day post-treatment with 2.5mg extract/kg b.w. (Figure 2).

Table 1. Effect of leaf aqueous extract of *C. mollis* on body weight gain along the experimental period in goats naturally infected with gastrointestinal nematodes

Groups/treatment	Untreated group		Doramectin group		*C. mollis* treated group	
Time (day)	0	30	0	30	0	30
Body weight (kg)	14.8±2.9	15.7±3.0	13.5±3.1	16.6±2.9	15.5±2.7	17.4±2.5*
Baseline gain weight	13.2-16,4	13.9-17.4	11.7-15.2	14.9-18.2	13.9-17.0	15.9-18.8

Each value represents the mean n=12. Values are means ± standard deviation. An asterisk mark represents significant diference; *P*<0.05. Differences were analyzed by Students t-tests. Negative control (untreated group), positive control (doramectin treatment).

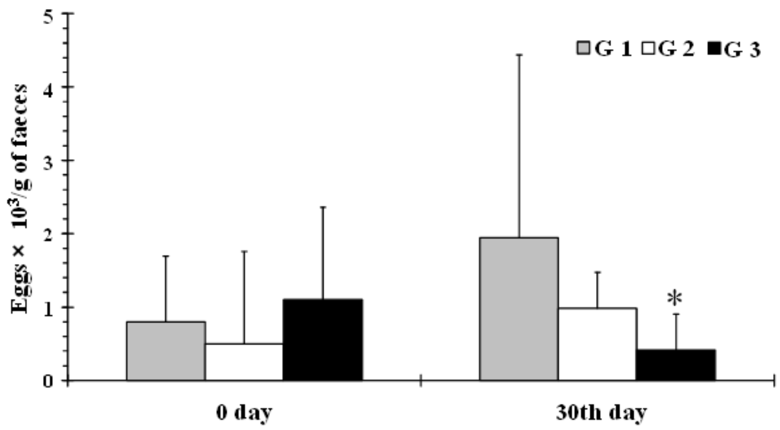

Figure 2. Effect of *Cratyliamollis* leaf decoction extract (on mean number of nematode egg per gram of faeces in naturally infected goats. Values are means ± standard deviation. An asterisk mark represents significant differences, *P*<0.05. G1: Negative control (untreated), G2: Positive control (treated with doramectin, 1mL/50 kg b.w.), G3: animals treated with 2.5mg/kgof extract

Regarding serum antibody responses, the Figure 3 shows the serum immunoglobulin average concentration between trial animal groups. It was observed that the levels of IgA response remained high in the treated group with the *C. mollis* decoction extract (Figure 3A), showing a significant difference (*P*<0.05) compared to untreated animals (negative control). On the other hand, the IgG stayed at low levels in the trial group treated with *C. mollis* extract (Figure 3B) (*P*<0.05), regarding the No-treated and doramectin control groups with high IgG of serum concentration.

Although some results remained stable throughout the experiment without any difference for all groups, as noted with some haematological parameters, such as PCV values, leukocyte and haemaglobin counts, others evaluated aspects in the extract post-treatment, nevertheless, showed significant differences when compared to the

negative and positive control. However the eosinophils count remained high after the *C. mollis* extract treatment.
Animals treated with *C. mollis* extractgained more body weight than the controls, untreated and doramectin groups. However, differences between all groups were not statistically significant, the average values of animal gain body weight were correlated to the low faecal egg count in extract treated group compared to control groups.

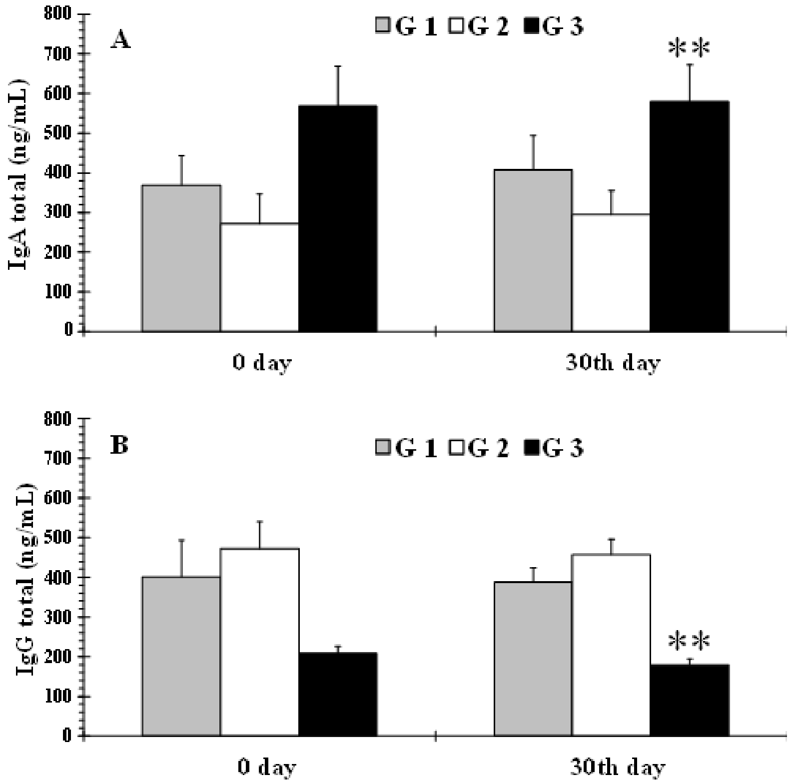

Figure 3. Effect of *Cratyliamollis* leaf decoction extract on mean concentrations of serum IgA (A) and IgB (B) response in goats naturally infected with gastrointestinal nematodes. Values are expressed as means ± standard deviation. Significant differences are indicated by asterisk mark (P<0.001). G1: Negative control (untreated), G2: Positive control (treated with doramectin, 1mL/50 kg b.w.), G3: animals treated with 2.5mg/kgof extract

Parasitological results at the post-treatment indicated that the extract exhibited anthelmintic activity in naturally infected goats, as evidenced by the FEC decrease in*C. mollis* treated group compared to untreated group. Regarding the high FEC values deviations, this can be explained on the basis of two situations 1). goatswere grazing under the Brazilian semi-arid region traditional extensive management, therefore always exposed to a contaminated environment, and 2).there are in thesusceptibility of animals to nematode infection(BISHOP, 2015; COUTINHO et al., 2015).

A possible explanation for the FEC reduction may due to the direct effect of theextract on the decrease of fecundity of female parasites. According to David, J.M. (personal communication), some phenolic compounds were determined in the leaf extract, such as flavonoids, flavans, norsesquiterpene and coumarins, beyond two steroids (megastimanes and ergostane) (LIMA et al., 2009). So, the effects resulting from this treatment could be explained by the presence of phenolic compounds in *C. mollis* leaf decoction extract, especially tannins that can affect the nematode fecundity, once several studies support the role of these compounds as antiparasitic agents (MOLAN et al., 2003; CHAN-PÉREZ et al., 2016). However, this activity may also be related to the presence of megastimanes and ergostane steroids, considering that steroidal saponins have been reported to have anthelmintic activity (ATHANASIADOU et al., 2001; DOMINGUES et al., 2010). Indeed, our experimental results are consistent with *in vitro* and *in vivo* studies conducted to determine anthelmintic effects of polyphenol compound towards different gastrointestinal nematodes, suggesting that this plant extract activity could be attributed to polyphenol capacity to bind to proteins, hindering the transcuticular absorption of nutrients, which cause in larvae starvation and death (CUNHA et al., 2011).

In accordance with other studies, the mechanisms by which an extract can inhibit the microbial growth are varied and can be due in part to the hydrophobic nature of some of its components. These molecules can interact with the lipid bilayer of the cell membrane and affect the respiratory chain and the production of energy, leading to the interruption of intracellular signalling cascades vital for cellular functions (LEWANDOWSKA et al., 2013; CHAN-PÉREZ et al., 2016), which can affect various targets, where the different therapeutic components collaborate in a synergistic effect, having greater anthelmintic activity than the purified individual constituent (CORNARA et al., 2016).

Relative to the humoral immune response, a significant rise in the total IgA was observed in the animal treated with the extract, whereas IgG level remained low in the same group when compared to control groups. This result indicates that IgA response plays an important role involved in the protective immunity against gastrointestinal nematodes, once the FEC count remained low.

So, IgA and eosinophils act synergistically against nematode infection, once this parameter remained high. In accordance with De la Chevrotière et al. (2012), these parameters could increase the ability of host defense against parasites, as many studies suggested that these cells and IgA play a role in resistance to this infection. Eosinophils are considered to be important elements against helminth infection and immune response (BALIC et al., 2000; FINLAY et al., 2016).

With respect to the phenolic compound, there is now emerging evidence that the plant metabolites exert immunomodulatory roleon systemic and intestinal compartments through selective actions on different components of the intracellular signalling cascades vital for cellular functions (ABUELSAAD et al., 2013).For example, a protective immunity against parasites was noted in animals treated with polyphenols. The therapeutic efficacy ofphenolics might be attributed to their stimulatory effects on the production of antibodies (OKAZAKI et al., 2010;Kaleemet al., 2014; KILANI-

JAZIRI et al., 2016), leading to weight gains, FEC reduction and high IgA. That is consistent with our experimental results.
Although more research is necessary, these results, therefore, are in agreement with the hypothesis that IgA and eosinophil levels interact to regulate nematode infection. Trial results also suggest a possible association between phenolic and other compound content andthe observed potential anthelmintic properties of *C. mollis* leaf decoction extract. However, the *C. mollis* leaf extract holds potential as an effective treatment in goats. Therefore, further *in vitro* and *in vivo* studies should be carried out with this extract to determine the optimal administered dose and to explain these results.

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