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A Review on the Anti-Toxocara Effect of Different Plant Extracts

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Abstract

Toxocara canis and *Toxocara cati* are important zoonotic parasites of dogs and cats. The increasing use of medicinal plants as anti-parasitic agents are attributed to their advantages such as less side effects, with lower risk of anthelmintic resistance, and a cheaper alternative. Although there are still no reports on anthelmintic resistance in *Toxocara spp*, the tendency of it happening should always be anticipated. This review summarized the *in vitro* and *in vivo* studies of the anti-*Toxocara* activity of plants, to enumerate the different plant extracts and the isolated active compounds in relation to their activites. *In vitro* studies were primarily done in *Toxocara larvae*, mostly second-stage larvae, while *in vivo* studies were performed in animals mainly to assess the effect of the plant extracts on larval migratory behavior. Among the all plants described in this review, family *Asteraceae* were the most investigated for their anthelmintic activities against *Toxocara* species. The isolated active compounds with promising results were pyrethrin, kaurenes, palasonin, certain piperamides and curcuminoids, asarone, ascaridole, quercetin, thymohydroquinone (TQ), and other secondary metabolites like flavonoids, alkaloids, tannins, saponins, and glycosides. However, the mechanism of action of each active ingredient of the plant as an anti-toxocara requires further research.

Keywords: anthelmintic, cats, dogs, animal laboratory, medicinal plants, *Toxocara spp*

Review Efek Ekstrak Tanaman Berbeda sebagai Anti-Toxocara

Abstrak

Toxocara canis dan Toxocara cati adalah parasit zoonosis yang sering menyerang anjing dan kucing. Meningkatnya penggunaan tanaman obat sebagai agen antiparasit disebabkan karena keunggulannya yaitu minimal efek samping berbahaya, risiko resistensi anthelmintik yang lebih rendah, dan murah. Meskipun masih belum ada laporan resistensi anthelmintik pada Toxocara spp, namun hal ini harus selalu diantisipasi. Ulasan ini merangkum studi in vitro dan in vivo dari zat aktif tanaman sebagai anti-Toxocara, dari berbagai ekstrak tanaman dan metode isolasi senyawa aktif berkaitan dengan kemampuannya. Studi in vitro secara umum dilakukan pada larva Toxocara spp tahap kedua, sedangkan studi in vivo dilakukan pada hewan untuk mengetahui efek ekstrak tanaman terhadap migrasi larva. Di antara semua tanaman yang dijelaskan dalam ulasan ini, famili Asteraceae merupakan tanaman yang paling banyak dipelajari aktivitas anthelmintiknya terhadap spesies Toxocara spp. Senyawa aktif yang bertanggung jawab diantaranya pyrethrin, kaurenes, palasonin, piperamida dan kurkuminoid, asaron, ascaridole, quercetin, thymohydroquinone (TQ), serta metabolit sekunder seperti flavonoid, alkaloid, tanin, saponin, dan glikosida. Mekanisme kerja masing-masing bahan aktif tanaman sebagai anti-toxocara memerlukan penelitian lebih lanjut.

Kata kunci: obat cacing, kucing, anjing, hewan laboratorium, tanaman obat, Toxocara spp

Introduction

Infection with *Toxocara canis* and *Toxocara cati* in puppies and young dogs may be fatal, but rarely a cause for concern in the health of adult dogs. Toxocariasis in humans, on the other hand, may result in visceral or ocular larva migrants and may cause inflammation of the airways (Peregrine, 2014; Nijsse et al., 2014). Toxocariasis in companion animals occurs worldwide with an overall global prevalence of 11.1% in dogs, and pooled global prevalence of 17% in cats (Rostami et al., 2020a, Rostami et al., 2020b). Contamination of the environment with Toxocara eggs plays an important role in the oral transmission of toxocariasis to other dogs, cats, and humans. Anthelmintic treatment of dogs and cats with patent toxocariasis is key to preventing environmental contamination as embryonated T. eggs, which are shed through animals' feces, are resistant to common disinfectants like bleach, and adverse

environmental conditions (Overgaauw and van Knapen, 2013; Moorhead, 2019).

Generally, there are two ways to investigate a plant's activity; either by letting the infected animal ingest plant parts and then observing the effects, or by examining medicinal plant extracts *in vivo* and *in vitro* (Athanasiadou et al., 2007). Although there are still no reports of anthelmintic resistance in Toxocara species (Gilleard, 2019), the tendency of it happening should always be anticipated. This review article generally aims to enumerate the different plant extracts tested for their activity against *Toxocara spp.* eggs and/or larvae from 1968 to 2020; and specifically, aims to compare these different plant extracts in terms of their efficacy and safety. In this study also we seen how the active compound responsible for each plant's.

Discussion

Plants with Potential Anti-Toxocara Activity, either for direct consumption as herbal or traditional medicine or for experimental purposes, usually involves plant extraction. In an experimental setup, medicinal plants are prepared first by proper and timely collection of the plant, authentication by an expert, adequate drying, and grinding" (Abubakar and Haque, 2020). Plants from the family Asteraceae, followed by Amaryllidaceae, Arecaceae, Papaveraceae, and Fabaceae were often frequently studied for their anthelmintic activity against *Toxocara spp*. The investigated plants from this family were *Chrysanthemum cinerariaefolium, Vernonia amygdalina, Cichorium intybus, Artemisia absinthium, Mikania glomerata, Mikania laevigata, and Vernonia cinerea*. Artemisia absinthium prepared by Yildiz et al. (2011), they were extracted its flower and oil using diethyl ether, while Ramos et al. (2015) used hydro alcohols. Mikania glomerata and M. laevigata were dried and extracted with ethanol (Zamprogno et al. 2015). Klimpel et al. (2010) obtained extracts of the Allium cepa via ethanol, methanol, water, and chloroform, while Orengo et al. (2016a) only used ethanol and water as solvents for plant extraction in their in vitro study, and only ethanol in their in vivo investigation. Sales et al. (2012), on the other hand, used powdered herbs of A. sativum; and Orengo (2016) used ethanol and water as solvents for A. sativum bulbs.

Studies of anti-antitoxin activity were summarized in this article. Most of the *in vitro* studies were performed against Toxocara second-stage larvae. Zamprogno et al. (2015) used ethanol extracts of Euterpe edulis, Mikania glomerata, and M. laevigata in all their different concentrations (0.1 mg/mL, 1 mg/mL, 10 mg/mL) showed inhibitory effects on the embryogenesis of Toxocara canis eggs after 15 days of interaction. This suggests that these extracts may be used in controlling T. canis eggs. Additionally, the research by Orengo et al. (2016a) proved the ethanol extract of Allium cepa to be effective in inhibiting hatching of 100% of T. canis eggs between 10000 and 1250 ug/mL through egg hatch assay, which is different from the effect of the ethanol extract of Allium sativum on the development of T. canis eggs at same concentrations. Specifically, A. cepa and A. sativum ethanol extracts were both most effective at concentration of 78.13 ug/mL with a percentage egg hatch/ development inhibition of 72% and 68%, respectively. Meanwhile, only the water extract of A. cepa showed moderate effects on T. canis eggs. Ethanol extracts of these three plants were proven to be more effective at 17 lower concentrations than their water extract counterparts, but overall, the ethanol extract of A. cepa showed better dose response. Even though the results from A. cepa and A. sativum extracts are comparable to commonly used anthelmintic drugs like benzimidazoles, they are still not as active as the combination drug Vermic Total™.

The research on the embryonic and larval development of T. cati eggs by Hussein and Shukur (2020) revealed that 25 mL of pumpkin seed oil added onto extracted eggs halted the development of the eggs until their two-cell stage with a rate of 61.9% at the first week of incubation and 43.2% at the fourth. A total 35.7% of the eggs remained undeveloped in the first week. This suggests that Cucurbita pepo has a potential for an efficient and effective anthelmintic against T. cati. Unfortunately, Artemisia absinthium extract did not show inhibition of larval development in the embryonated Toxocara cati eggs mixed with two different concentrations of the extract with distilled water (0.3 mg/mL, 0.6 mg/mL) since the larvae developed 21 days post-treatment.

El-Sayed (2017) investigated the viability, embryogenesis, and infectivity of non-embryonated Toxocara canis eggs at 1000

eggs/mL incubated with 25, 50, and 100 mg/mL of Zingiber officinale ethanol extract at 25°C for 6, 12, and 24 hours for assessment of viability, and for 2 weeks for assessment of the plant extract's effect on embryogenesis. The 18 experiments showed that Z. officinale has 98.2% efficacy on ovicidal activity on T. canis eggs, wherein it was best observed at 100 mg/mL concentration after 24 hours. This may have been due to improved diffusion of the extract through the eggshell as time passes by that in turn further promotes the action of zingibain contained in the plant. The differences in the effects between concentrations and controls were found to be dependent on the concentration and time, hence, the concentrationor dose- and time-dependent effects of Zingiber officinale. Furthermore, the plant extract showed 99.64% efficacy on the inhibition of embryogenesis of T. canis eggs and caused degeneration at 100 mg/mL concentration 2 weeks after treatment.

Ediriweera and colleagues (2018) determine the anti-Toxocara effect of Gyrinops walla, particularly its effectiveness against infective larvae. In this experiment, levamisole acted as positive control, and phosphate buffer solution as negative control. The decoction of G. walla was found to be 80.25% effective in inhibiting Toxocara larval migration versus 99.7% in levamisole. Moreover, Ediriweera et al. (2020) revealed that water extract of Vernonia cinerea has 89.42% larval migration inhibition, which is lower than the 99.7% with the use of levamisole. Hussein and Shukur (2020) tells that pumpkin seed oil exhibits high anthelmintic efficacy against T. cati as the rate of live larvae was 38.2% and dead larvae was 61.75% at the first week, and 12.8% and 87.17%, respectively, at the second week. This study suggests that pumpkin seed oil is a more efficient anthelmintic agent against T. cati than Artemisia absinthium extract used in the study by Yildiz et al. (2011). Yildiz et al. (2011) found that only the number of parasitic eggs was decreased but no inhibition of larval development when A. absinthium extract was used. To sum it up, G. walla and V. cinerea are effective in inhibiting larval migration, and Cucurbita pepo is effective in inhibiting larval development, together with inhibiting egg development.

Spiegler et al. (2020) showed that the hydroethanolic extract of P. pinnata is lethal in T. cati third-stage larvae, with T. cati being sensitive with lethal concentration (LC50) of about 112 ug/mL. The experimentation involved solutions of ten to 20 larvae incubated with the extract in different concentrations ranging from one to 1000 ug/mL. Then, mortality was assessed 72 hours after incubation by addition of 50 uL of hot water first before observation of any motility. The studies by Mata-Santos et al. (2015) and Ramos et al. (2015) did not indicate the stage of larvae they used for their in vitro experiments. Mata-Santos et al. (2015) revealed in their study that the isolated compounds from Tabebuia sp. extract that are four of the 17 phenazines, lapachol, and three of its derivatives at 2 mg/mL concentration presented a 100% larvicidal or larvistatic activity based on their larval mobility. The best of which were nor-lapachol (minimal lethal concentration, MLC, 1 mg/mL), lapachol (MLC 0.5 mg/mL), B-lapachone, and B,C-allyl-lawsone 24 (MLC 0.25 mg/mL). Minimal lethal concentration (MLC) refers to the lowest concentration with an RM value of 0 after 24 hours of incubation. However, the four phenazines referred to did not yield good results when exposed to low concentrations.

On the other hand, Ramos et al. (2015) evaluated the anthelmintic activity of the hydroethanolic extracts of *Aloe vera, Argemone mexicana, Artemisia absinthium, Centrosema virginianum, Chenopodium ambrosioides*, and *Carica* papaya via calculation of larval RM every 24 hours for 72 hours, and the cytotoxic activity on MRC-5 cells (human fetal lung fibroblast cells). Among which, A. mexicana and *C. papaya*, in which hydroethanolic extracts are rich in alkaloids, caused RM to be down to less than 80% 72 hours post-incubation with 100 ug/mL of the extract, hence, they could be considered active against the parasite. Neither exhibited cytotoxicity on MRC-5 cells, while A. vera, A. vulgaris, C. virginianum, and C. ambrosioides did not show any activity against the parasite. *Pycnanthus angolensis* seemed to be the most effective plant extract against Toxocara larvae at lowest concentration, with 0.1 mg/mL of its ethanol and methanol extracts having higher nematocidal activity than albendazole after 2 days of exposure. Similar results were found in the use of hydroethanolic extract of *Argemone mexicana* and *Carica papaya* but these require 1 mg/mL and 3 days of incubation. Isoquinoline alkaloids isolated from *Macleaya cordata* and

Chelidonium majus, and isolated compounds from Tabebuia species showed promising results as well but the isoquinoline alkaloids were found to have high cytotoxicity. Additionally, asarone from *Acorus calamus* showed only temporary and reversible inhibition, hence, at least 18 hours or longer exposure is needed to attain permanent RM inhibition. Furthermore, only *Gyrinops walla* and *Vernonia cinerea* were assessed for their larval migration, wherein they were found to be effective; and only *Paullinia pinnata* was used for thirdstage larvae that it was found that 0.1 mg/mL concentration of the hydroethanolic plant extract was lethal in this stage of T. larvae. Inversely, no anti-Toxocara effect were observed in Piper nigrum, *Aloe vera*, *Aloe vulgaris, Centrosema virginianum*, and *Chenopodium ambrosioides*. Against *Toxocara spp*. adult worms *Caesalpinia bonduc* fixed oil of the seeds showed significant dosedependent anthelmintic activity against *Toxocara canis* as evident in the immobility of the worms after being exposed to different concentrations of the fixed oil, especially at 100 mg/mL. This was followed by petroleum ether extract, ethanolic extract, and water extract of the C. bonduc leaves in terms of activity leading to the paralysis and death of worms.

Shalaby et al. (2018) examined the anti-Toxocara effect of the methanolic extract of Balanites aegyptiaca fruit via observation of the cuticle of the adult T. canis worms after 24 and 48 hours of incubation in Ringer's solution containing 240 ug/mL of the extract under a scanner electron microscope. Main changes observed 24 hours post-incubation revealed wrinkled cuticular surface of the anterior region of the worms, whereas 48 hours post-incubation showed deformed sensory papillae and more pronounced wrinkling of the cuticular surface of the worms, which supposedly should make the worms inside a dog's intestine vulnerable leading to their expulsion in relation to depression of their activity.

Salas and colleagues (2012) did their in vivo experiment on adult dogs. First, the dogs were dewormed using an oral broad-spectrum conventional anthelmintics (12.5 mg milbemycin, 125 mg praziquantel). After one week, a fecalysis was conducted to test the drugs' efficacy which came out to be 100% efficacious. One group among the treated groups of dogs were fed ad libitum with supplemented diet containing powdered herbs of Allium sativum, Mentha piperita, Ulmus fulva, Thymus vulgaris, Galium aparine, Urtica dioica, Picrasma excelsa, Capsicum minimum, Cinnamomum zelandicum, Foeniculum vulgare for eight months. Fecal samples from these particular dogs were again examined at six and eight months after treatment with conventional anthelmintics. At eight months post-treatment, the treated group fed with the supplemented diet came out negative for T. canis as compared to the treated group that was not provided with the supplemented diet. Also, this treated group fed with supplementation had decreased FEC. The point is that a herbal blend supplemented diet could aid in controlling T. canis infection in dog populations not dewormed regularly.

Another study on cats was the one by Yildiz et al. in 2011 that involved 11 two- to threeyear-old naturally infected cats who were orally given diluted Artemisia absinthium extract with doses of either 300 mg/kg BW or 600 mg/kg BW, depending on which group they were assigned to, once a day for seven days. Yildiz et al. (2011) used flotation technique with saturated salt solution to evaluate the fecal samples pre-, during, and post-treatment period, up to eight days after completion of extract administration. It was detected that FEC gradually decreased in cats belonging to Group 1, and that deformed bodies of the worms in feces were seen. To further assess the activity of A. absinthium extract not only to the worms but as well as to the body of the treated group, levels of ALT, AST, ALP, BUN, and creatinine were measured and it was determined that the values were within 30 normal limits, and that this plant may serve as an alternative choice in treatment of parasites. This means, too, that A. absinthium extract was well tolerated by the cats. But the higher dose of 600 mg/kg BW of A. absinthium extract yielded better results with general reduction in FEC in all cats examined that may be related to the egg-laying potential of T. cati being reduced by A. absinthium extract. Four of the nine in vivo studies in dogs and cats included complete blood count as a basis for the effectiveness of the different plant extracts against Toxocara species.

Hassanain et al. (2015) did their experiment on puppies naturally infected with T. canis. Treatment plan was to give either mebendazole alone, Citrus aurantifolia alone, or a combination of the two for three

consecutive days for two weeks. The results revealed that the highest efficacy was achieved by the combination of the two medications, producing a significant decrease in FEC (98.2%). But what is more interesting is the gradual decrease in FEC that occurred from the end of the first week of treatment to the end of one week after treatment, while the blood values like HgB concentration, RBC count, PCV, WBC count, total protein, and albumin concentration during and after treatment and recovery came out within normal limits, particularly in those receiving the combined therapy.

Orengo and colleagues (2016b) collected fecal samples from their subjects, which are eight- to ten-week-old puppies, a day before treatment and on days one, three, five, seven, ten, and 14 after treatment to determine eggs per gram (EPG) via McMaster technique. Anthelmintic efficacy of the Allium cepa bulb extract was evaluated by computation of percentage FECR (%FECR) with the help of the pretreatment and posttreatment EPG counts. Aside from that, hematological parameters were also noted on days zero, seven, and 14 post-treatments.

The study by Ulloa et al. (2013) yielded favorable results because they found that the hydroalcoholic extract of Coriandrum sativum seeds at concentration of 0.5 and 1.0 mg/mL has the ability to inhibit infectivity caused by completely embryonated eggs (L2) in BALB/c mice. The animals were specifically necropsied 12 days after infection and treatment for evaluation of larval migration wherein they did not find any larvae in any of the organs of the treated mice. In the study by El-Nahas et al. (2020), the experimentally infected mice were either treated with Cassia nodosa ethanolic extract alone, albendazole alone, or the combination of both. The combination therapy gave the highest reduction percentage in larval recovery (93.2%), followed by the ethanol extract alone (69.45%), and then, albendazole (44%); that there were no seen larvae in the lungs, liver, or muscles in all treated groups, only in the brain. All the treatment medications used prevented intense inflammation and degeneration of the liver and lungs. Further, the plant extract presented better control of the pathology than what albendazole did. Overall, the combination therapy led 37 to enhancement of the anti-parasitic efficacy up to 93.2%.

Whereas in the study by El-Refai et al. (2017), it was found that N. sativa oil mixed with albendazole showed the highest larval reduction percentage (83.7%) at 45 days post-infection as compared to the two other treatment groups: with albendazole alone and with N. sativa oil alone, which by the way also both showed significant larval reduction percentage of 66% and 62%, respectively. The 83.7% larval reduction percentage is close to that recorded by Musa et al. in their study in 2011 (87%). Factors such as use of different N. sativa preparations and infectious egg loads may have contributed to the different results achieved from the two studies. Besides, *N. sativa* oil was observed to be able to reduce the *T. canis* larvae-induced pathological lesions and inflammation, but it was the combination of *N. sativa* oil and albendazole that showed nearly normal histology of the examined tissues. Another thing, all the treated mice groups in the study of El-Refai et al. (2017) were observed to have increase in their IL-4 and IFN-y serum levels, and improvement in terms of immune 39 response as evidenced by the increasing specific anti-Toxocara IgG and IgG1 levels.

Three herbal methanolic extracts and one allopathic immunomodulator were used by Moudgil et al. (2012) to evaluate their effect on the migratory behavior of T. canis larvae in tissues of Swiss albino mice. These mice were experimentally infected with T. canis embryonated eggs 14 days post-medication with either of the mentioned immunomodulators. Another 14 days after infection, mice were euthanized and necropsied for larval migration studies. This was repeated 28 days post-infection. The collective results revealed that Hippophae salicifolia was the superior immunomodulator, followed by *H. rhamnoides*, then the allopathic immunomodulator levamisole, and finally *Piper longum*.

The efficacy of the ethanol extracts of Allium cepa and A. sativum were also not tackled in the two research of Orengo et al. (2016a), and there was no establishment of the effectiveness of Balanites aegyptiaca fruit in killing the parasites according to Shalaby et al. (2018), and the efficiency of pumpkin seed oil as an anthelmintic herbal medicine in infected cats and dogs (Hussein and Shukur, 2020). On the other hand, no toxicity studies were conducted from the methodologies of all the

retrieved articles, especially in the study by Yildiz et al. (2011) since they used the bittertasting Artemisia absinthium; and in the study by Mata-Santos et al. (2015) wherein quinones, which could be significantly toxic, are found to be present in Tabebuia species. Lastly, there were not enough comparative studies between conventional and alternative treatment for toxocariasis.

Among the articles retrieved online, only the research of Beletini et al. (2019) was related to an in vivo study of the anti-Toxocara activity of a plant in the environment. Their study involved Moringa oleifera seed extract as a coagulant in raw and distilled water that would aid in the reduction of infective eggs, therefore, increasing the free non-infecting larvae in these waters. Basically, they first added 800 eggs L-1, where about 95% were non-embryonated, into 1000 mL each of raw and distilled water samples prior to the coagulation process. When the plant extract was added at 10, 30, and 50 mg L-1, they analyzed the samples via quantitative polymerase chain reaction as for egg removal and viability. Moringa oleifera seed extract was able to reduce the infective eggs in the water samples that the reduction of eggs reached 99-100%, which may also be due to the eggs' high density. Then, the number of free noninfecting larvae increased, which is a good result as well. This could be because of the thin layer of coagulant on the eggs having to cause larvae to hatch earlier, hence, the reduction in environmental contamination as the eggs are not embryonated just yet prior to hatching. Consequently, M. oleifera caused a reduction of turbidity in raw water by 66-72.2%. In other terms, the reduction in the egg viability of Toxocara eggs also implies that transmission of toxocariasis will be lower. Some other advantages of *M. oleifera* seed extract as a coagulant are it being useful, inexpensive, and biodegradable. Interestingly, the use of *M. oleifera* resulted in a lower rate of viable eggs than when the more common aluminum sulfate was used. Finally, it was worth noting that the higher the concentration of the coagulant, the lower the proportion of viable eggs; and despite some of the eggs being non-infecting, majority of the eggs still remain infective post-coagulation process with *M. oleifera*.

Conclusion

The top five plant families with the most frequently studied plant species for anthelmintic activity against Toxocara species were Asteraceae, Amaryllidaceae, Arecaceae, Papaveraceae, and Fabaceae. Nearly all studies showed promising results in terms of their anti-Toxocara activity, but conventional medications like albendazole still remain more effective. Nevertheless, the anthelmintic activity against Toxocara species in companion animals could be improved by supplementation or combination with some plant extracts. Also, there is a need for further studies to identify the mode of action of each plant component because understanding them may help in the modification and enhancement of the plant extracts' efficacy and safety for use in animals, and even in humans.

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