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# CURCUMIN IN TREATMENT OF EXPERIMENTAL TRICHINOSIS

By
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**Abstract**

*Trichinella spiralis* is one of the most widespread zoonotic parasitic nematodes in the world. There is an increasing interest in developing new safe and effective anthelminthic herbal drug against *T. spiralis*. This study assessed the effect of curcumin (bioactive compound of *C. longa*) in treatment of *T. spiralis* infected mice compared with albendazole. Seventy-five albino mice were classified into four groups. GI: Non-infected control, GII: Infected non-treated control, GIII: Treated early 3rd dpi by albendazole alone, curcumin alone, and combination of albendazole & curcumin, and GIV: Treated on 31st dpi by the same drugs. Mice were sacrificed on the 7th dpi for intestinal phase assessment and on the 49th dpi for muscle assessment. Treatment efficiency was assessed by parasitological and histopathological examinations. The results showed a significant decrease in intestinal adults' count in all treated groups compared to non-treated cont rolones. Reduction rates of the intestinal phase were 92.87% in albendazole & curcumin treated group followed by 87.58% in albendazole treated group and 62.93% in curcumin treated group. There was also significant decrease in muscle larvae count compared to positive control ones by reduction rates of 84.03%, 70.38% & 44.96% for albendazole &curcumin, albendazole alone and curcumin alone respectively. The histopathological results showed improvement in intestinal and muscular architecture in all treated groups compared to positive control one, particularly in combined albendazole & curcumin treated group.

**Keywords**: Mice, *Trichinella spiralis*, Curcumin, Albendazole.

## Introduction

Trichinellosis is a cosmopolitan zoonotic infectious disease caused by *T. spiralis*, with economic problem in swine production and food safety (Morsy *et al*, 2022). Human infection is caused by ingestion of raw or insufficiently cooked meat from pigs or other infected animals (Fahmy *et al*, 2021). All *T. spiralis* development stages are in same host and so this parasite was used as a model to estimate efficacy many anthelmintic (Bruschi *et al*, 2019).

Despite the availability of effective and relatively safe drugs such as albendazole and mebendazole for the treatment of trichinellosis, these drugs have several drawbacks, such as the emergence of parasite drug resistance (Vercruysse *et al*., 2007), poor absorption of drugs in the intestinal lumen due to their low solubility and limited activity against encapsulated parasite larval stages (Kalaiselvan *et al*, 2007). They are also contraindicated in children less than three years of age and during pregnancy (Yadav and Temjenmongla, 2012). Thus, there was an increasing need for safe and effective drugs, especially from medicinal herbs, which are less toxic and almost have no adverse effects (Basyoni and El-Sabaa, 2013).

*Curcuma longa*, known as tumeric, is one of the most widely used medicinal plants. It belongs to genus *Curcuma*, family Zingiberaceae. It contains polyphenolic curcuminoid compounds, such as diferuloylmethane and curcumin, which give the plant its therapeutic value (Cheraghipour *et al*, 2018). Curcumin has a highly pleiotropic molecule interacting with numerous inflammatory molecular targets, as anti-inflammatory, anticancer, antioxidant, anti-atherosclerotic, antibacterial, antiviral, and antifungal (Hussein *et al*, 2021), as well as anti-protozoa activity as *Giardia lamblia* (Pérez-Arriaga *et al*, 2006), cerebral malaria (Waknine-Grinberg *et al*,

2010), anti-*Trypanosoma brucei* (Gressler *et al*, 2015), anti-*Leishmania* (Cheikh-Ali *et al*, 2015), and anti-*Schistosoma mansoni* (Hussein *et al*, 2017).

This study aimed to evaluate the efficacy of curcumin (bioactive compound of *C. longa*) in treatment of *Trichinella spiralis* infected mice as compared to albendazole.

## Materials and Methods

This study was carried out in Biological Unit, Theodor Bilharz Research Institute, from August 2022 to December 2022.

Parasite: *T. spiralis* strain was isolated from infected pigs' diaphragm in El-Basatine Governmental Abattoir, Cairo. Parasite was kept by regular repeated mice passages. Muscles of mice heavily infected with *T. spiralis* were cut and digested in a solution of 1% pepsin & 1% Hcl in 37°C water bath. After an overnight incubation, larvae were extracted by the sedimentation technique, washed several times in normal saline, and number of larvae/ml was counted by a hemocytometer. Each mouse was infected orally by 200 larvae using a blunt tuberculin syringe (Wassom *et al*, 1988).

Drugs: 1- Albendazole® (Alzental) suspension was purchased from Pharma Cure Pharmaceutical Industries Co. as 400mg/10ml given orally in a dose of 50mg/kg/day. *2*- Curcumin with piperine 500mg capsule: Each capsule contained 500mg *C. longa* & 2.5mg piperine from EVA Pharma for Pharmaceutical & Medical Appliances, Giza, suspended in distilled water for oral suspension at a dose of 150mg/kg/day.

Experimental design: Seventy-five clean laboratory bred male Swiss Albino mice; 8-10 weeks old; ~20-25g in weight were classified into 4 main groups GI: Non-infected non-treated (negative control). GII: Infected non-treated (positive control), which was subdivided into two subgroups: GIIa: Sacrificed 7$^{th}$ day post infection (dpi) and GIIb: Sacrificed 49$^{th}$ dpi. GIII: Infected and treated early in the disease course (3$^{rd}$ dpi) for 3 successive days and sacrificed 7$^{th}$ dpi. GIII was subdivided into three subgroups: GIIIa: Treated with albendazole alone at a dose of 50mg/kg/d. GIIIb: Treated with curcumin alone at a dose of 150mg/kg/d. GIIIc: Treated with combination of curcumin at a dose of 150mg/kg/d and albendazole at a dose of 50mg/kg/d. GIV: Infected and treated from 31$^{st}$ dpi for 7 successive days and sacrificed 49$^{th}$ dpi, which was subdivided into three subgroups: GIVa: Treated with albendazole alone. GIVb: Treated with curcumin alone. GIVc: Treated with combination of both curcumin and albendazole.

Parasitological examination: a- Intestinal phase, adults were collected from the small intestine, and counted, & b- Muscular phase, muscle larvae were recovered by artificial digestion, and counted.

Histopathological examination: a- Intestinal phase, sections from intestine, & b- Muscular phase, sections from diaphragm and thigh muscles, were fixed in 10% buffered formalin solution, dehydrated, cleared, and embedded in paraffin sections of 5µm thickness, stained with (H&E) and microscopically examined for pathological changes caused by adults in intestine and larvae in muscles. Stained sections were assessed for degree of inflammation, and number of lymphocytes, plasma cells and neutrophils, classified to mild, moderate, and intense reaction (Drury and Wallington, 1980).

Ethical considerations: The protocol was approved by the Research Ethics Committee, Faculty of Medicine, Benha University, Egypt, approval number: MS181121. Mice were handled according to National Research Centre guidelines (NRC, 2011).

Statistical analysis: Data were tabulated and analyzed by Computer Program SPSS (Statistical package for social science) version 20. Analysis was conducted by Student's *t*-test &ANOVA test. Parasite reduction % in was calculated: R% = 100(C-E)/C, where R%: (Reduction %) C: Control and E: Experimental (Penido *et al*, 1994).

## Results

A significant decrease in intestinal adult worms' count was found in all treated groups

compared to infected non-treated control group. Albendazole and curcumin treated mice showed least mean count (7.0±1.58) with highest reduction rate (92.87%) as compared to positive control (98.2±6.83) and both albendazole treated mice (12.2±1.92) with a reduction rate of (87.58%), and curcumin treated mice (36.4± 5.55) with a reduction rate of (62.93%).

All treated mice showed a significant decrease in muscle larvae count compared to positive control. Albendazole and curcumin treated mice gave least mean count (1520.0 ±238.75) with high reduction rate (84.03%) as compared to positive control (9520.0± 1227.6) and both albendazole treated mice (2820.0±408.66) with reduction of (70.38%) and curcumin treated mice (5240.0 ±626.9) with a reduction rate of (44.96%).

Details were given in tables (1 & 2) and figures (1, 2, 3, 4, 5, 6, 7, 8, 9, 10 & 11).

Table 1: *T. spiralis* adults' count recovered from intestine among groups (7th day post infection).

| Groups (10 mice in each) | Mean± SD | P value | R% |
|---|---|---|---|
| Positive control | 98.2± 6.83 | bcd | -- |
| Albendazole treated | 12.2± 1.92 | ad <0.001** | 87.58% |
| Albendazole+ curcumin treated | 7.0± 1.58 | ad <0.001** | 92.87% |
| Curcumin treated | 36.4± 5.55 | abc <0.001** | 62.93% |

P <0.001**: highly significant versus control, b significance with albendazole treated, c significance with albendazole+ curcumin treated, d significance with curcumin treated.

Table 2: *T. spiralis* larval recovered from muscles among groups (49thday post infection).

| Groups (10 mice in each) | Mean± SD | P value | R% |
|---|---|---|---|
| Positive control | 9520.0± 1227.6 | bcd | - |
| Albendazole treated | 2820.0± 408.66 | acd <0.001** | 70.38% |
| Albendazole+ curcumin treated | 1520.0± 238.75 | abd <0.001** | 84.03% |
| Curcumin treated | 5240.0 ± 626.9 | abc <0.001** | 44.96% |

Histopathologically: Small intestinal sections of positive control mice on 7th dpi showed adult worm sections embedded within intestinal villi, a distorted villous pattern and severe inflammation. Intestinal sections of mice treated with albendazole and curcumin showed the best result in the form of preserved villous pattern, healthy intestinal villi with a core of connective tissue, normal epithelial covering and mild inflammation. But, intestinal sections of mice treated with curcumin showed improvement of villus architecture and mild inflammation, but intestinal sections of mice treated with albendazole showed preserved villous pattern with moderate inflammation.

Muscle sections of positive control mice on 49th dpi showed multiple depositions of encysted larvae embedded in muscle and intact capsules surrounded by intense inflammatory cellular infiltrate. Sections of skeletal muscle of mice treated with albendazole showed fewer number of encysted larvae (some with degenerated capsules) surrounded by mild inflammation. Skeletal muscle of mice treated with albendazole and curcumin showed much fewer numbers of encysted larvae and the capsule around the larvae showed thinning and vacuolation, degeneration of larva with mild invasion by the inflammatory cells. Sections of skeletal muscle of mice treated with curcumin revealed fewer numbers of encysted larvae with some degeneration of the larvae capsule surrounded by mild inflammation.

## Discussion

Trichinellosis is a food-borne parasitic disease caused by eating raw or undercooked pig meat containing infective larvae of *T. spiralis* (Rainova *et al*, 2016). In Egypt, it has been documented in man, and in fresh and processed pork (Dyab *et al*, 2019).

In the present study, in the intestinal phase, the effect was evaluated based on the adults count in the small intestine and the histopathology of intestinal tissue. In the muscular phase, the effect was evaluated by the total larval burden in muscles and histopathology of muscular tissue. There was a significant decrease in mean number of adults in all treated mice compared to positive control ones on the 7th dpi. Albendazole & cur-

cumin treated mice gave the high reduction in worm count (92.87%) followed by albendazole treated mice (87.58%) and lastly curcumin treated mice (62.93%). This agreed with Hamed *et al.* (2022) in Egypt, who reported a significant decrease in mean number of adults in all treated groups compared to positive control. Mice received curcumin 150mg/kg alone for 3 successive days started on 3rd dpi gave a significantly lower intestinal worm reduction 32.99%. The lowest intestinal worm burden was in the mice given albendazole 50mg/kg alone or combined with curcumin 150mg/kg for 3 successive days from 3rd dpi, where R% in each group was 90.78%. However, the present curcumin effect on adult burden was more than that reported by Hamed *et al.* (2022). They dissolved curcumin in normal saline in spite of the fact that curcumin has low bioavailability. But in the present study, the piper was added to curcumin, which markedly increased its bioavailability. This agreed with Elguindy *et al.* (2019) in Egypt, who reported that infected mice received curcumin alone 100mg/kg/day dissolved in distilled water started 2 hours after infection and continued for ten successive days showed a significant decrease in mean number of adults in treated mice compared with positive control ones. Meanwhile, also Elguindy *et al.* (2019) dissolved curcumin in distilled water as Hamed *et al.* (2022) did without adding anything to increase its bioactivity Turrini *et al.* (2020) in Italy reported that *Piper nigrum*, the king of spices, is one of the most popular worldwide as a source of bioactive molecules with pharmacological properties.

In the present study, all treated mice showed a significant decrease in muscle larvae as compared to positive control ones on 49th dpi. Albendazole & curcumin treated mice recorded the highest reduction rate of encysted *T. spiralis* larvae (84.03%) followed by albendazole treated mice (70.38%) and the least was curcumin treated ones (44.96%). This agreed with Hamed *et al.* (2022), who reported that mice received curcumin 150mg /kg for 3 weeks, started on first week post infection gave a significantly lower larval reduction rate of 23.46%. Mice given albendazole 50mg/kg alone or combined with curcumin 150mg/kg for 3 weeks, showed a reduction rate in larval count of 56.49% & 58.42%, respectively. Administration of a higher curcumin dose (300mg/kg) for the same time and duration was the most efficacy in reducing muscular larval count (70.67%). But, in the present study, curcumin on muscle larvae burden was more effective. This agreed with Elguindy *et al.* (2019), who reported that infected mice received curcumin alone as 100mg/kg/day dissolved in distilled water started on 2 hours after infection, continued for ten successive days and on 35th dpi, showed an extremely significant reduction of total larval counts in infected treated mice as compared to positive control with reduction rate of (53%). The differences in curcmin killing larvae may be due to the fact that Elguindy *et al.* (2019) started treatment 2 hours after infection, which killed most of the adults during the intestinal phase and led to decrease in larval count in muscles. This also agreed with Atia *et al.* (2021) in Egypt, who reported that both curcumin and curcumin-nano at a dose of 50mg/kg for 5 days started 13th dpi, showed that the larval reduction rate of 41.06% & 62.19% respectively**.**

In the present study, intestinal sections of infected control mice on 7th dpi showed the adults' sections embedded within the intestinal villi, a distorted villous pattern and severe inflammation. Intestinal sections of albendazole and curcumin treated mice showed the best efficacy in form of preserving villous pattern, healthy intestinal villi with a core of connective tissue, normal epithelial covering and mild inflammation. However, intestinal sections of mice treated with curcumin showed improvement of villus architecture and mild inflammation, but intestinal sections of mice treated with albendazole showed preserved villous pattern with moderate inflammation. This agreed with Hamed *et al.* (2022), who reported that combined

curcumin (150mg) and albendazole treatment showed healthy intestinal villi with a core of connective tissue, normal epithelial covering, intact brush border, and few goblet cells. Albendazole-treated mice showed improvement in intestinal villous architecture with moderate infiltration with inflammatory cells. Curcumin 150mg-treated mice showed moderate sub-epithelial inflammatory infiltration and few embedded larvae. Curcumin 300mg-treated group showed intact intestinal villi and mild cellular infiltrate. This agreed with Elguindy *et al.* (2019), who reported that small intestinal sections of infected curcumin treated mice showed same histopathological changes, but with a marked increase in the inflammatory reaction surrounding the adults compared with the positive control one. However, this last item disagreed with the present study that showed mild inflammatory reaction considering curcumin as anti-inflammatory. Dehzad *et al.* (2023) in Iran reported that turmeric/curcumin supplementation might be used as a viable intervention for improving inflammatory/oxidative status of individuals.

In the present study, muscle sections of positive control mice on 49$^{th}$ dpi showed multiple depositions of encysted larvae embedded in muscle and intact capsules surrounded by intense inflammatory cellular infiltrate. Skeletal muscle of mice treated with albendazole showed fewer number of encysted larvae (some with degenerated capsules) surrounded by mild inflammatory cellular infiltrate. Skeletal muscle of albendazole and curcumin treated mice showed negligible numbers of encysted larvae. Skeletal muscle of curcumin treated mice showed few numbers of encysted larvae with degeneration of larvae capsule surrounded by mild inflammation. This agreed with Hamed *et al.* (2022), who reported that albendazole treated mice showed degenerated larvae surrounded by dense inflammatory cells. Curcumin 150mg-treated group showed moderate muscle inflammatory infiltration. The curcumin 300mg-treated group showed marked improvement with completely degenerated larvae and minimal inflammatory cells. Curcumin 150mg and albendazole treated group showed degenerated larvae invaded by inflammatory infiltration. This agreed with Elguindy *et al.* (2019), who reported that muscle sections of curcumin treated mice showed much fewer numbers of encysted larvae, besides the capsuled larvae showed splitting, thinning, and vacuolation. However, there was a marked increase in the inflammatory reaction surrounding the larvae compared with the infected control group and this disagrees with our results that showed mild inflammatory reaction surrounding the larvae in the curcumin treated group. White *et al.* (2019) in USA concluded that curcumin didn't decrease several inflammatory in patients with chronic inflammatory diseases.

## Conclusion

Curcumin was effective against the intestinal and muscular stages of *T. spiralis* in experimentally infected mice with addition of piper, but less effective than albendazole. For human use, piper might be contraindication with peptic ulcer. The histopathology was a good tool for assessment of the drug efficacy in trichinosis treatment.

*Authors' contributions:* They declared that they equally contributed in the field and lab activities.

*Conflict of interest:* Authors declared that they neither have especial interest nor received any fund.

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**Explanation of figures**

Fig. 1: Intestinal section of control non-infected group, showed normal histological structure (H & E, X200).

Fig. 2 : Intestinal section of positive control group on 7th dpi, showed cut section in adult embedded within intestinal villi (red arrow), a distorted villous pattern (black arrow) and severe inflammation (yellow arrow) (H&E, x200).

Fig. 3: Intestinal section of albendazole treated group on 7th dpi, showed improved villous pattern (black arrow) and moderate inflammation (red arrow) (H&E, x200).

Fig. 4: Intestinal section of curcumin treated group on 7th dpi, mostly preserved villous pattern (black arrow) and mild inflammation (red arrow) (H&E, x200).

Fig. 5: Intestinal section of albendazole & curcumin treated group on 7th dpi, preserved villous pattern (black arrow) and mild inflammation (red arrow) (H&E, x200).

Fig. 6: Muscle section of control non-infected group, showed normal histological structure (H & E, x100).

Fig. 7: Skeletal muscle section of positive control group (red arrow) on 49th dpi, showed multiple depositions of encysted larvae embedded in muscle and intact capsules (yellow arrow) surrounded by intense inflammatory cellular infiltrate (black arrow) (H&E, x100).

Fig.8: magnification of Fig. 7 (H&E, x200)

Fig. 9: Skeletal muscle section of albendazole treated group (red arrow) 49th dpi, showed fewer number of *T. spiralis* encysted larvae (yellow arrow) (some with degenerated capsules) (blue arrow) surrounded by mild inflammatory cellular infiltrate (black arrows) (H&E, x400).

Fig.10: Skeletal muscle section of curcumin treated group (red arrow) 49th dpi, showed fewer numbers of encysted larvae (yellow arrow) with some degeneration of larvae and capsule (blue arrow) surrounded by mild invasion of inflammatory cells (black arrows) (H&E, x400).

Fig. 11: Section of skeletal muscle (red arrow) of the albendazole & curcumin treated group 49th dpi, showing much fewer numbers of larvae (yellow arrow), vacuolation of the larvae (blue arrow) and degeneration of larvae and capsule with mild invasion by inflammatory cells (black arrows) (H&E, x400).A, b, c….must be as A size .