Effectiveness of immature *Mangifera indica* Linn (mango) fruit in reducing the *Ascaris lumbricoides* infection among children: a non-inferiority randomized controlled trial

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Abstract

Introduction This study aimed to compare the effectiveness of immature *Magnifera indica* L. (mango) fruit with albendazole in reducing *Ascaris lumbricoides* infection among children.

Methods Children aged 2 to 14 years were enrolled in a randomized, controlled, non-inferiority trial. Participants were randomly allocated to receive 250 mL immature mango fruit puree daily for 3 days or one dose of albendazole 400 mg tablet. Egg reduction rates and cure rates were computed and compared. Adverse effects were monitored during and after administration of treatment.

Results There was a statistically significant decrease between the pre- and post-treatment EPG of those who took immature mango fruit ($p < 0.001$) and those who took albendazole ($p < 0.001$). There was a higher ERR and CR for the albendazole group, but the difference was not significant ($p = 0.472$, $p = 785$, respectively). Risk analysis of reduction in intensity showed mango is non-inferior to albendazole (RR = 0.80, 95% CI 0.67, 0.97; $p = 0.026$). Risk analysis of cure showed mango is non-inferior to albendazole in both PP (RR = 0.92, 95% CI 0.68, 1.25; $p = 0.607$) and ITT (RR=0.79, 95% CI 0.58, 1.08; $p = 0.139$).

Conclusion Immature *Mangifera indica* Linn is non-inferior to albendazole in terms of effectiveness in the reduction of ascariasis infection.

Keywords: Ascariasis, soil transmitted helminthiasis, helminth, mango

Soil transmitted helminthiasis (STH) is a group of parasitic infections which can be caused by *Ascaris lumbricoides* (intestinal roundworm), *Trichuris trichiura* (whipworm), and *Necator americanus* or *Ancylostoma duodenale* (hookworm).[1] According to the World Health Organization (WHO), STH is classified as a neglected tropical disease. STH infections worldwide are confirmed to be over 1 billion, with another 4.5 billion individuals at risk of infection, and school-age children considered as the highest risk group.[2-4] Ascariasis is the most common STH infection.[5] These STH infections occur largely in areas with inadequate sanitary disposal facilities and poor water supply.[1] In the Philippines, a baseline survey revealed that provincial regions across the country have a

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prevalence of STH infections above 50%.[6] The Philippine government's response to address this issue has been the Department of Health's (DOH) Soil Transmitted Helminth Control (STC) Program. The STC Program attempts to deworm millions of children across the nation on a biannual basis, through the administration of albendazole. The WHO also handles its deworming programs with similar and traditional drugs.[1]

Research regarding natural alternative treatments for STH has gained attention due to the possibility of drug resistance to current therapy for STH.[7] Studies show that synthetic antihelminthics generally used are not very safe because of their side effects and toxicity. The increase in helminth infection and their growing resistance to most broad-spectrum chemotherapeutics is a major problem facing human health.[8,9] Reports also show antihelminthic resistance due to frequent use of drugs. Factors that have led to the development of antihelminthic resistance were incorrect dosing, widespread use and increased frequency of treatment. Hence, there is a need for development and discovery of new substances that are derived from plants having antihelminthic properties.[7]

This study evaluated the capacity of *Mangifera indica* Linn (mango) as a natural, alternative treatment for ascariasis. Relatively inexpensive and readily available in the Philippines, mangos are an ideal candidate for study and a potential alternative to current treatment. Potential antihelminthic attributes of plants such as *Mangifera indica* L., and their extracts are credited to secondary metabolites, such as alkaloids, terpinoids or polyphenols.[10] A polyphenol found in aqueous extracts of *Mangifera indica* L. known as tannin is largely responsible for antihelminthic action.[11] Additionally, flavonoids found in mango can potentially be applied as larval growth inhibitors as well.[11]

The general objective of this study is to determine the effectiveness of immature *Mangifera indica* L. fruit in the reducing Ascaris lumbricoides infection among children aged 2-14 years compared to albendazole. Specifically, this study aimed to 1) determine the egg reduction rate (ERR) in children taking immature mango fruit compared to those taking albendazole; 2) determine the cure rate (CR) in children taking immature mango fruit compared to those taking albendazole; and 3) determine the hazard ratio of any adverse effects experienced by children taking immature mango fruit compared to those taking albendazole.

Methods

This was a randomized, controlled, non-inferiority trial. The sampling population consisted of residents of Barangay San Isidro Labrador, Rodriguez, Rizal, aged 2 to 14 years. Enrolled in the study were all those who submitted an assent form and whose guardians submitted a consent form, had not undergone treatment with antihelminthic drugs for the past month, and positive for ascariasis during baseline analysis. Those with co-existing infections (cough, colds, fever) during the study, had known allergy to either treatment modality, gastroesophageal disease, and known autoimmune diseases were excluded. Participants were randomly allocated to receive immature mango puree or albendazole. Each participant was assigned an identification code that was written on a piece of paper, placed in a bowl, and randomly drawn and alternately assigned to treatment groups. Sample size was based on 91% cure rate of immature mango fruit, with confidence level set at 95%, alpha error at 1.96, and level of precision at 0.05.[12]

Demographic data consisting of age, sex, average family income, height, and weight were collected from each participant using a survey form patterned according to the World Health Organization (WHO) recommended survey, STH and Schistosomiasis School Survey Child Form. Stool samples were collected for pre-treatment analysis. Kato-Katz technique was used to analyze one fecal smear per participant. Pre-treatment egg counts were obtained and used to classify the intensity of ascariasis infections into light (1-4,999 epg), moderate (5,000-49,999 epg), or heavy (≥50,000 epg) infections based on the WHO guidelines.

Participants were then randomly allocated to treatment groups. The control group received a single dose of albendazole 400 mg tablet. The experimental group received 250 mL immature mango fruit puree, prepared fresh each morning, each day for three consecutive days. Guardians of participants helped in assuring proper compliance with the treatments. Stool samples were collected from each participant after one month and analyzed using the Kato-Katz technique. All participants from either treatment group who were still found positive during post-treatment analysis were administered a single dose of albendazole 400 mg tablet.

Participants who were not able to provide a stool sample for post-treatment analysis were considered dropouts. Egg reduction rates (ERR) and Cure Rate (CR) were computed to assess the antihelminthic effectiveness of immature mango fruit puree. percentage drop of post-treatment mean EPG from pre-treatment mean EPG, measured after the administration of treatment. The egg reduction rate was the percentage drop of post-treatment mean EPG from pre-treatment mean EPG, measured after the administration of treatment. Cure was indicated by the absence of A. lumbricoides eggs in one post-treatment fecal smear processed by the Kato Katz technique. Adverse effects were monitored during and after administration of treatment. Guardians were advised to contact the investigators for any untoward symptoms during the one-month interval between pre-treatment and post-treatment analysis.

Analysis was performed using Stata 14 statistical software. T-test or Wilcoxon-Shapiro Test, and chi-square were used to compare demographic data (age, sex, average family income, height, and weight), pre- and post-treatment egg count, ERR and CR. The risk ratios for both ERR and CR, respectively, were computed in per protocol (PP) and intention-to-treat (ITT) worst-case scenario analysis to account for the effect of dropouts. All dropouts in the immature fruit puree group were assigned as not having reduced EPG or not cured status while those in albendazole group as having reduced EPG or cured status for the worst-case scenario analysis. For ERR analysis, the change in intensity of infection of each participant of both treatment groups was considered. Only those who experienced a decrease in intensity of infection were noted as having reduction. Decrease corresponded to at least one-degree reduction on the intensity of infection. Those without at least one degree decrease in intensity or had an increase in intensity were noted as having no reduction even in the presence of actual reduction in mean EPG.

The research was approved for implementation by the UERMMMCI Research Institute for Health Sciences Ethics Review Committee. The researchers obtained informed consent, and assent as applicable, from all participants. Measures were taken to ensure the privacy and confidentiality of the children-participants.

Results

A total of 96 children were enrolled in study of which 6 and 3 children were dropped from the immature mango fruit and albendazole groups, respectively. The baseline socio-economic demographics and clinical characteristics, as summarized in Table 1, indicate that both treatment groups were comparable at the start of the trial.

Table 1. Comparison of baseline characteristics of immature mango (n=46) and albendazole (n=41) groups.

Demographic Characteristic	Immature Mango Fruit Group	Albendazole Group	p-value
Sex (n (%)			0.240
Male	26 (56.5)	18 (43.9)	
Female	20 (43.5)	23 (56.1)	
Age (yr)			
Mean ±SD	6.5 ± 3.22 (95% CI 5.54, 7.46)	6.5 ± 3.61 (95% CI 5.37, 7.65)	0.942
Weight (kg)			0.446
Mean ±SD	19.2 ± 6.71 (95% CI 17.16, 21.14)	17.8 ± 5.20 (95% CI 16.11, 19.40)	
Height (cm)			0.882
Mean ±SD	110.3 ± 19.84 (95% CI 104.42, 116.21)	110.4 ± 20.56 (95% CI 103.89, 116.87)	
Average family income (PHP)			0.258
Mean ±SD	8693.48 ± 5897.81 (95% CI 6942.04, 10444.91)	9146.34± 4323.257 (95% CI 7781.75, 10510.93)	
Initial EPG	7857.7 ± 16232.86 (95% CI 3037.15, 12678.28)	8592.9 ± 11833.93 (95% CI 4857.68, 12328.18)	0.249

There was a statistically significant decrease between the pre- and post-treatment EPG of those who took immature mango fruit ($p < 0.001$) and those who took albendazole ($p < 0.001$), as seen in Table 2. Table 3 shows a higher ERR and CR for the albendazole group, but the difference was not significant ($p = 0.472$, $p = 0.785$, respectively).

Risk analysis of reduction in intensity showed mango is non-inferior to albendazole in intention-to-treat (ITT) analysis but a statistically significant inferiority in per protocol (PP) analysis, implying that the results were altered by the dropouts. Tables 4 and 5. Summarize the total subjects with and without reduction in both treatment groups. Meanwhile, risk analysis of cure showed mango is non-inferior to albendazole in both PP and ITT analysis.

Tables 6 and 7 summarize the total cured subjects in both treatment groups. Thus, immature mango fruit puree is found non-inferior to albendazole in terms of effectiveness in reduction of ascariasis infection; but is not non-inferior in terms of CR.

No adverse effects were recorded for both treatment groups.

Table 2. Comparison of mean pre- and post-treatment EPG in immature mango and albendazole groups.

Treatment Group	Pre-treatment (Mean ± SD)	Post-treatment (Mean ± SD)	p-value
Immature mango fruit	7857.7 ± 16232.86 (95% CI 3037.15, 12678.28)	2319.1 ± 6916.53 (95% CI 265.20, 4373.06)	p < 0.001
Albendazole	8592.9 ± 11833.93 (95% CI 4857.68, 12328.18)	732.3 ± 1723.96 (95% CI 188.14, 1276.44)	p < 0.001

Table 3. Comparison of ERR and CR in immature mango and albendazole groups.

	Immature Mango Fruit	Albendazole	p-value
ERR	86.7% ± 0.24	93.9% ± 0.12	0.472
CR	63.04%	68.29%	0.785

Table 4. Comparison of reduction in intensity of infection in both treatment groups (per protocol analysis).

Treatment Group	Participants with Reduction in EPG	Participants without Reduction in EPG	RR (95% CI)	p-value
Immature mango fruit	38	8	0.92 (0.78, 1.08)	0.303
Albendazole	37	4		

Table 5. Comparison of reduction in intensity of infection in both treatment groups (worst case scenario analysis).

Treatment Group	Participants with Reduction in EPG	Participants without Reduction in EPG	RR (95% CI)	p-value
Immature mango fruit	38	14	0.80 (0.67, 0.97)	0.026
Albendazole	40	4		

Table 6. Comparison of CR in both treatment groups (per protocol analysis).

Treatment Group	Participants Cured	Participants not Cured	RR (95% CI)	p-value
Immature mango fruit	29	17	0.92 (0.68, 1.25)	0.607
Albendazole	28	13		

Table 7. Comparison of CR in both treatment groups (worst case scenario analysis).

Treatment Group	No. of Participants Cured	No. of Participants not Cured	RR (95% CI)	p-value
Immature mango fruit	29	23	0.79 (0.58, 1.08)	0.139
Albendazole	31	13		

Discussion

The anthelmintic ability of the immature mango is attributed to the phytochemicals, specifically the polyphenols present in the pulp. Polyphenols are present in mango puree concentrate and have been characterized through high precision liquid chromatography (HPLC) with diode array and mass spectrometric detection.[13-15] Among the polyphenol subclasses, phenolic acids (gallic acid and apeginin) and flavonoids (tannin, mangiferin, gallotannins, quercetin, isoquercetin, ellagic acid, and β-glucogallin) exhibit anthelmintic properties.[16,17] One kilogram of immature mango fruit contains a total phenolic content of 27.8 ± 2.21 mg GAE/g which contains 20mcg/mL tannin, 4.4 mg/kg mangiferin, and 6.9 mg/kg gallic acid.

Among the polyphenols, tannin has the most potent anthelminthic property.[17] Tannin and its other form, condensed tannin (CT) or proanthocyanidin, has the capacity to bind to the cuticle of infective larva that can lead to decreased nutrient availability, causing larval starvation and death.[17,18] The tannins bind to the site of the cuticle crucial for transport of non-nutrient organic solutes, and other small organic molecules.[18] The cuticle serves as a highly impervious barrier between the host and its environment. It maintains the body morphology and integrity, and has a critical role in locomotion and uptake of nutrients of helminths.[19] As the tannin binds to the cuticle of the larva, it interferes with energy generation by inhibiting or dissociating the 'coupling' or 'joining' of the electron transport and the phosphorylation (uncoupling oxidative phosphorylation) reactions resulting in inhibition of ATP synthesis, immobilization and starvation, and eventually the death of the larva.

A study by Williams showed that extracts which had the greatest number of CT were the most potent against *Ascaris suum*, as evidenced by a reduced migratory ability of newly hatched third-stage larvae, and reduced motility and survival of fourth-stage larvae recovered from pigs. *A. suum* is similar to *A. lumbricoides* and is even suggested to be of the same species.[20,21] Another study by Niezen reported that feeding a diet with CT in lambs inhibited the effects on the egg hatching of *Trichostrongylus colubriformis*. These findings indicate that CT can be detrimental to both egg hatching and larval development by reducing migration and motility, suggesting that CT can have a marked effect on the subsequent development of nematode larvae.[22] A study by Terrill showed that CT is not absorbed in the digestive tract since none was detected in the blood of sheep and all were found in the digestive tract. Therefore, these CT are all concentrated in the feces, which have more effects on the hatchability of the eggs.[14] Condensed tannins are currently the most studied natural class of compounds for reducing egg counts in ruminants infected with gastrointestinal nematodes such as *Ascaris lumbricoides*.[23]

In vivo and in vitro studies by Nery have indicated anthelmintic effects, specifically the inhibition of larval development and fecal egg count reduction, against mixed ovine gastrointestinal nematodes.[13] Tannins and flavonoids were the primary metabolites identified in the phytochemical analysis of the extracts of unripe M. indica L. var. Uba. Another in vitro test of aqueous extracts of immature mango showed effective inhibition of larval development at a concentration of 50 mg/mL and the metabolite extracts were mostly proanthocyanidin (CT), hydrolysable tannin, triterpenes and saponins. Another study used chestnut tannin solutions in geometrical scale concentrations from 0.32 to 20.48 g/L, which significantly reduced nematode egg hatching.[24]

The induction of mangiferin also leads to a significant decline in the number of helminths during the larval stages. Moreover, mangiferin is observed to inhibit the production of reactive oxygen species including nitrous oxide that mediates the intestinal pathology of the helminths. The inhibition of the production of reactive oxygen species may have affected the adult female embryogenesis.[25]

Gallic acid, which is found in significant amounts in mango pulp, and apigenin has similar mechanism of action as tannin.[25] Gallic acid causes a dose dependent paralysis and death of *Pheretima phostuma* (earthworm), and at least 10 mg of gallic acid was needed to produce this effect. *Pheretima phostuma* and *Ascaris lumbricoides* share the same collagenous cuticle structure. The apigenin, on the other hand, can also inhibit larval growth. Kawasaki showed inhibition of larval growth in *Caenorhabditis elegans* (roundworm) was associated with DAF-16 activation. Apigenin acts as a stressor to either stimulate DAF-16 activity directly or inhibit DAF-2/insulin signaling, which reduces the inhibitory effect of DAF-2 on DAF-16. In either case DAF-16 is activated, and eventually leading to larval arrest.[26]

In contrast to the polyphenols, the prime effect of albendazole is flaccid paralysis of ascaris, which allows easier expulsion of the worms by gastrointestinal peristalsis. Albendazole increases the chloride ion conductance of worm muscle membrane, which produces hyperpolarization and excitability reduction, which leads to flaccid paralysis of worms.[26]

Both experimental and standard treatments for ascariasis showed significant decrease in infection. After administering for 3 days, the experimental treatment of immature mango fruit puree had 86.68% ERR, while the standard treatment, albendazole, showed 93.93% ERR. In addition, the CR of immature mango fruit puree is 63.04% while albendazole is 68.29%. These values are consistent with that obtained by Belizario wherein the CR of standard drug, albendazole, against ascariasis was 69.7%.[6] The ERR and the CR of immature mango fruit puree are high and comparable to that of albendazole.

The RR for reduction of intensity is only significant upon ITT analysis. The dropouts in the study, however low, affected the results. Meanwhile, there is no difference in RR for cure rate in both PP and ITT analysis. The cure rate of immature mango fruit puree was comparable to albendazole. This can be due to rapid reinfection of *A. lumbricoides*. Numerous studies showed that rapid reinfection of *A. lumbricoides* was observed post-treatment even with standardized chemotherapy against *A. lumbricoides* infection.[27-29] Upatham compared the predisposition to reinfection of different intestinal helminths after chemotherapy.[30] The results showed that A. *lumbricoides*, as compared to hookworms and *T. trichiura*, has the strongest predisposition to reinfection; it occurs very rapidly in children that live in tropical countries and are younger than 15 years of age.

In conclusion, immature mango puree was found to be non-inferior to albendazole in terms of effectiveness in reduction of ascariasis infection.

References

1. WHO. What are intestinal worms (soil transmitted helminthiasis)? World Health Organization. Available from: http://www.who.int/intestinal_worms/disease/en/. [Cited 2016 Sep 1].
2. Jia TW, Melville S, Utzinger J, King CH, Zhou XN. soil transmitted helminth reinfection after drug treatment: a systematic review and meta-analysis. PLOS. 2012 May.
3. Scolari C, Torti C, Beltrame A, Mateelli A, Castelli F, Gulletta M, Ribas M, Morana S, Urbani C. Prevalence and distribution of soil-transmitted helminth (STH) infections in urban and indigenous school children in Ortigueira, State of Parania, Brasil: implications for control. Trop Med Int Health 2000; 5(4): 302-7.
4. Gyorkos TW, Maheu-Giroux M, Blouin B, Casapia M. Impact of health education on soil-transmitted helminth infections in school children of the Peruvian Amazon: a cluster-randomized controlled trial. PLoS Negl Trop Dis 2013; 7(9): e2397.

5. Sabin Vaccine Institute. Ascariasis. Available from: http://www.globalnetwork.org/ascariasis. [Cited 2016 Sep 1].
6. Belizario V, De Leon W, Wambangco M, Esparar D. Baseline assessment of intestinal parasitism in selected public elementary schools in Luzon, Visayas and Mindanao. Acta Med Philipp 2002; 39(2): 11-21.
7. Mohan C, Saxena N, Fozdar BI. Activity of indigenously known angiospermic plants against common GI parasites of livestock. World J Pharm Pharmaceut Sci 2015; 4(9): 1652-67. Available from: https://www.wjpps.com/download/article/1441367821.pdf
8. James CE, Davey MW. Increased expression of ABC transport proteins is associated with ivermectin resistance in the model nematode Caenorhabditis elegans. Int J Parasitol 2009; 39: 213-20.
9. James CE, Davey MW. A rapid colorimetric assay for the quantification of the viability of free living larvae of nematodes in vitro. Parasitol Res 2007; 101(4): 975-80.
10. Cowan MM. Plant products as antimicrobial agents. Clin Microbiol Rev 1999; 12(4): 564-82.
11. Martinez-Micaelo N, González-Abuín N, Ardèvol A, Pinent M, Blay MT. Procyanidins and inflammation: molecular targets and health implications. Biofactors 2012; 38(4): 257-65.
12. El-Sherbini G, Osman, S. Antihelminthic activity of unripe *Mangifera indica* L (mango) against Strongyloides stercoralis. Int J Curr Microbiol Appl Sci 2013; 2(5): 401-9.
13. Nery PS, Nogueira FA, Oliveira NJF, Martins ER, Duarte ER. Efficacy of extracts of immature mango on ovine gastrointestinal nematodes. Parasitol Res 2012; 111(6): 2467-71. doi: 10.1007/s00436-012-3017-4
14. Terrill T, Waghorn GC, Wooley DJ, McNabb WC, Barry TN. Assay and digestion of 14C-labelled condensed tannins in the gastrointestinal tract of sheep. Br J Nutr 1994; 72(3): 467-77.
15. Masibo M, He Q. Major mango polyphenols and their potential significance to human health. Compr Rev Food Sci Food Saf 2008; 7(4): 309-19. doi: 10.1111/j.1541-4337.2008.00047.x
16. Schieber A, Ullrich W, Carle R. Characterization of polyphenols in mango puree concentrate by HPLC with diode array and mass spectrometric detection. Innov Food Sci Emerg Technol 2000; 1(2): 161-6.
17. Iqbal Z, Sarwar M, Jabbar A, et al. Direct and indirect anthelmintic effects of condensed tannins in sheep. Vet parasitol 2007; 144(1-2): 125-31. Available from: https://www.researchgate.net/publication 6699277_Direct_and_indirect_anthelmintic_effects_of_condensed_tannins_in_sheep#pf7
18. Thompson DP, Geary T. Biochemistry and molecular biology of parasites. 1995. The structure and function of helminth surfaces, Available from: https://www.researchgate.net/publication/279607588_The_Structure_and_Function_of_Helminth_Surfaces
19. Page AP, Johnstone II. The cuticle. In: Kramer JM, Moerman DG, editors. Wormbook. The C. elegans Research Community; 2007. Available from: http://www.wormbook.org/chapters/www_cuticle/cuticle.pdf
20. Leles D, Gardner SL, Reinhard K, Iñiguez A, Araujo A. Are *Ascaris lumbricoides* and *Ascaris suum* a single species? Parasites & Vectors 2012; 5(1): 1.
21. Shao CC, Xu MJ, Alasaad S, et al. Comparative analysis of microRNA profiles between adult *Ascaris lumbricoides* and *Ascaris suum*. BMC Vet Res 2014; 10(1): 1.
22. Niezen JH, Waghorn GC, Graham T, Carter JL, Leathwick DM. The effect of diet fed to lambs on subsequent development of *Trichostrongylus colubriformis* larvae in vitro and on pasture. Vet Parasitol 2002; 105: 269-83
23. Ferreira D, Brandt EV, Coetzee J, Malan E. Condensed tannins. In: Progress in the chemistry of organic natural products 1999; 21-67. doi: 10.1007/978-3-7091-6366-5_2
24. Renco M, Sasanelli N, Maistrello L; Davis LM, editor. Nematodes: comparative genomics, disease management and ecological importance. 1st ed. New York: NOVA Science: 2014.
25. Garcia D, Escalante M, Delgado R, Ubeira FM, Leiro J. Anthelminthic and antiallergic activities of *Mangifera indica* L. stem bark components vimang and mangiferin. Phytother Res 2003; 17: 1203-08.
26. Kawasaki I, Jeong M-H, Oh B-K, Shim Y-H. Apigenin inhibits larval growth of *Caenorhabditis elegans* through DAF-16 activation. FEBS Lett 2010; 584: 3587-91.
27. Wiria AE, Hamid F, Wammes LJ, et al. The effect of three-monthly albendazole treatment on malarial parasitemia and allergy: a household-based cluster-randomized, double blind, placebo-controlled trial. PLoS ONE 2013; 8(3): e57899. doi: 10.1371/journal.pone.0057899
28. Yap P, Du Z-W, Wu F-W, et al. Rapid re-infection with soil-transmitted helminths after triple-dose albendazole treatment of school-aged children in Yunnan, People's Republic of China. Am J Trop Med Hyg 2013; 89(1). doi: 10.4269
29. Jia TW, Melville S, Utzinger J, King CH, Zhou XN. Soil transmitted helminth reinfection after drug treatment: A systematic review and meta-analysis. PLOS. 2012 May 8
30. Upatham E, Vivavant V, Brockelman W, Kurathong S, Lee P, Chindaphol U. Prevalence, incidence, intensity and associated morbidity of intestinal helminths in south Thailand. Int J Parasitol 1989; 19(2): 217-28.