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Hematological Profile in Schistosoma mansoni Infected Mice Treated with Commiphora molmol Extract Compared with Praziquantel

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Abstract

As Schistosoma mansoni worms inhabit the portal triad of infected hosts, deleterious changes were encountered in the blood picture. The aim of the study is to explore the damaging hematological effects due to S.mansoni infection in albino mice before and after treatment with either Commiphora molmol extract or Praziquantel. Seventy two albino mice were recruited in this study and divided into 4 groups of 18 mice each, 54 of them were infected with S.mansoni cercariae.7 weeks post-infection, infected animals were treated with 500 mg/kg either as a single dose for 2 days in Praziquantel or for 5 consecutive days in Commiphora molmol extract. Blood samples were collected at 1, 2 and 4 weeks after treatment for assessment of complete blood counts (Hb, erythrocytes count, haematocrite value, MCV, MCH, MCHC, Platelet count, leucocytic count and differential leucocytic counts). S. mansoni infection resulted in multiple damaging effects of the blood profile on infected non-treated hosts as evidenced by decrease in red blood cells and platelets and rise in white cells with the advance of infection. Treatment with Praziquantel corrected the blood profile of erythrogram and the platelet count in progressive manner with advance of time after treatment more than Commiphora molmol Extract. This study declared that Praziquantel and Commiphora molmol extract were safe drugs without dverse hematological effects on infected treated mice with more ameliorative action achieved by Praziquantel than Commiphora molmol extract.

Keywords: Blood picture, Mice, Mirazid, Praziguantel, Schistosoma.



INTRODUCTION

Schistosomiasis is one of the most widespread of the major parasitic diseases and its negative socio-economic and public health impact in tropical and subtropical regions of the world (WHO, 2007). Morbidity due to S.mansoni infection is mainly as a result of the host's responses to schistosome egg antigens to form granulomas mainly in the intestines and the liver where the eggs are trapped (Bindseli et al., 2004). The significant health problems associated with schistosomiasis include impaired cognitive amona primary school-age hepatosplenomegaly, anaemia, bladder cancer and stunted growth (Midzi et al., 2008). Also, genital schistosomiasis, which manifests at reproductive age if schistosomiasis is not treated, is attributed as a risk factor for HIV transmission (Feldmeier et al., 1994). The national policy on schistosomiasis control has adopted Praziguantel as the main drug of use to reduce morbidity. It is widely preferred owing to its safety, present low cost, accepted single dose with improved patient compliance, and efficacy against all five schistosome species (Deribew et al., 2013). About 66.5 million individuals infected with schistosomiasis (53.2 million school-aged children and 13.3 million adults) in 52 countries all-over the world mostly in African countries received PZQ treatment in 2015 (WHO, 2016).

Pharco Pharmaceuticals (Alexandria, Egypt) registered a drug under the name of (Mirazid, MZD) in 29 January 2002, as new innovative drug of natural origin for treatment of schistosomiasis in the form of soft gelatin capsule containing 300 mg of purified Commiphora molmol extract (myrrh) based on its effectiveness through many clinical and field studies delivered to the Egyptian ministry of health-drug policy planning center (Al-Kazzaz et al., 2017). previous studies. the drua showed antischistosomal activity as well as high safety profile on biochemical parameters but lower than PZQ (Al-Kazzaz et al., 2016; Al-Kazzaz et al., 2017a; Al-Kazzaz et al., 2017b; Aziz et al., 2017). The Baseline data about the hematological effects of schistosomiasis or its treatment with PZQ or MZD are scarcely available in the literature. This prompted us to study the hematological parameters in a murine model under the effect of schistosomiasis and its treatment with MZD in comparison with PZQ.

MATERIALS AND METHODS

This study was conducted in September 2014 and ended in January 2015.

MATERIALS

-Seventy two albino mice were brought from Safepharma research laboratory, New Borg El-Arab City, Alexandria, Egypt.

-Biomophalaria alexandrina snails infected with S.mansoni miracidia were purchased from Theodore Bilharz Research Institute, Cairo; Egypt.

-Praziquantel tablets (Batch No: 9118014) were purchased from a local pharmacy and Mirazid capsules (Batch No: 296) were obtained from Pharco Pharmaceuticals.

METHODS

Mice infection

Each mouse was infected with 100 *S.mansoni* cercariae by body immersion (Smithers and Terry, 1965). The *S.mansoni* cercariae were shedded from infected *B.alexandrina* snails after their exposure to flourecent light for about 1 hr then counted on a glass slide (Liang *et al.*, 1987). Mice were examined at 45 days after cercarial infection to investigate the presence of *S.mansoni* eggs in the stool (Khalil, 2000).

Study design

Mice were acclimatized for 1 week before test and only healthy animals were assigned to the present study. The drugs were administered after overnight fasting and eating was allowed after one hour. Treatment started 50 days' post infection. The study was carried out on 4 groups of 18 infected mice each. G1 was normal non-treated noninfected control group. G2 was non-treated infected control group. G3 was given PZQ (500 mg/kg for 2 days (Bakr et al., 2009). G4 was given MZD (500 mg/kg for 5 days) (Massoud et al., 2000). The animals were housed in a a controlled adequate environmental room with temperature (20 ±1°C), a relative humidity (50%-60%),12 light-dark cycles, and ventilation (more than 15 times/h). Mice were housed in separate cages and allowed free access to water and food according to the NRC guidelines (NRC, 2011).

Evaluation of the Hematological Parameters

Blood samples were withdrawn before sacrification of mice using capillary tubes introduced into the medial retroorbital venous plexus, a part of blood (about 300 ul) was collected into vacutainer tubes containing an anticoagulant (EDTA)] for determination of Complete Blood Count (CBC) (Sewify, 2009; Lewis *et al.*, 2006) by using haematology fully-automated cell counter (Mindray BC-3200).

Ethical considerations

The study protocol was reviewed and approved by the ethics committee of the medical research institute (MRI), University of Alexandria in October, 2014.

Statistical analysis

The data were coded, collected and analyzed using the independent two-sample t-test using Minitab statistical software, version 14 (Minitab Inc, Pennsylvania State College, Pennsylvania, USA). Descriptive statistics were expressed as arithmetic mean \pm SD as measures of central tendency and dispersion, respectively. The level of significance (P<0.05) was considered statistically



significant. Fisher's exact test was used to compare the difference in proportions between Mirazid and Praziquantel.

RESULTS AND DISCUSSION

Data presented in Table 1 showed that *S.mansoni*-infected mice presented with highly significant and progressive decrease (13%, 26.8% and 30.8%) in RBCs count, (27.5%, 46.6%, 59.4%) in the haemoglobin level and 21.6%,35.6% and 41.7% in the haematocrit value (HCT) in infected non-treated mice at 8,9 and 11 WPI respectively as compared to the non-treated mice. as well as

progressive decrease in red blood cell indices (9.7%, 12.8% and 25% in the MCV, 16.8%, 27.14% and 47.88% in the MCH and 7.5%, 17.2% and 30.33% in the MCHC at 8, 9 and 11 WPI as compared to the non-treated mice. Treatment with PZQ resulted in progressive increase in the RBCs count (4%,16.9% and 12.9%), HB level (11.9%,57% and 107.6%), HCT% (12.5%,40.1% and 42.5%), red blood cell indices [MCV (3.2%,20% and 26.2%), MCH (7.3%,34.12% and 83.9%) at 1,2 and 4 WPT and MCHC (12% and 45.7%) at 2 and 4 WPT, respectively as compared to the infected non-treated mice (Table 1).

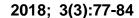
Table 1. Erythrocytes and their related indices in *S. mansoni*-infected mice under different treatments at different follow up periods.

Parameter /Group	WPT	Normal	Infected Non-treated	PZQ	MZD
HB (g/dl)	1	12.70±0.57	9.20±0.77A [-27.5%]	10.30±0.44b (+11.9%)	9.54±0.35 (+3.6%)
	2	13.26±1.00	7.07±0.90A [-46.6%]	11.10±0.61B (+57%)	10.25±1.0B (+44.9%)
	4	14.12±1.69	5.73±0.36A [-59.4%]	11.90±0.61B (+107.6%)	11.37±1.11B (+98.4%)
RBCs (10 ⁶ Cell/ul)	1	8.05±0.14	7.00±0.23A [-13%]	7.28±0.60 (+4%)	7.10±0.07 (+1.4%)
	2	8.20±0.48	6.00±0.27A [-26.8%]	7.00±0.67b (+16.9%)	6.90±0.73b (+15%)
	4	8.96±0.63	6.20±0.53A [-30.8%]	7.00±0.01b (+12.9%)	6.90±0.22b (+11%)
PCV (%)	1	40.82±1.30	32.00±3.21A [-21.6%]	36.00±1.81b (+12.5%)	32.00±1.15 (0%)
	2	42.40±1.95	27.30±2.60A [-35.6%]	38.27±1.12B (+40.1%)	31.00±2.55b (+13.5%)
	4	50.98±3.04	29.70±2.03A [-41.7%]	42.33±2.52B (+42.5%)	40.10±2.03B (+35%)
MCV (fl)	1	50.83±3.59	45.70±3.66a [-9.7%]	47.20±.02 (+3.2%)	45.00±2.55 (-1.5%)
	2	52.21±3.00	45.50±4.06a [-12.85%]	54.60±2.53B (+20%)	44.90±2.12 (-1.3%)
	4	64.04±3.68	47.90±4.10A [-25%]	60.47±2.03B (+26.2%)	52.70±2.57b (+10%)
MCH (pg)	1	15.81±0.61	13.14±1.02A [-16.8%]	14.10±1.05 (+7.3%)	13.40±0.81 (+1.9%)
	2	16.17±0.56	11.78±0.70A [27.14%]	15.80±1.46B (+34.12%)	14.80±0.57B (+25.6%)
	4	17.73±0.70	9.24±0.55A [-47.88%]	17.00±1.00B (+83.9%)	16.40±0.84B (+61.2%)
MCHC (%)	1	31.11±2.57	28.75±3.32 [-7.5%]	28.60±1.98 (-0.5%)	29.80±1.73 (+3.6%)
	2	31.27±1.85	25.89±2.07A [-17.2%]	29.00±1.86b (+12%)	33.00±1.58B (+27.4%)
	4	27.69±1.84	19.29±1.56A [-30.33%]	28.11±1.42B (+45.7%)	28.30±1.40B (+46.7%)

The statistical test used was independent two-sample t-test. Values were expressed as mean \pm SD. Numbers in parentheses indicate the percentage change, Numbers in parentheses [] indicate the percentage of change in relation to non-infected non-treated mice and Numbers in parentheses () indicate the percentage of change in relation to infected non-treated. a: Statistically significant at P < 0.05 compared to non-infected, A: highly significant at P < 0.01 compared to non-treated, b: Statistically significant at P < 0.05 compared to non-treated.

In the current study, infected mice showed significant elevation in WBC's counts (Leukocytosis) in a rate of 46.9% and 101.2% at 9 and 11 WPI respectively). Infected

non-treated group revealed progressive lymphocytosis in relation to the time of infection reaching 38.8% at 4 WPI. Neutropenia was evident in an ascending manner in





response to infection in non-treated mice in a rate of (24%,33.3% and 62.1%) at 8,9 and 11 WPI. Monocytes and basophils were not significantly changed in infected non-treated mice at both 1,2 or 4 weeks' post-infection. PZQ treatment resulted in non-significant decrease in WBCs count (10.8%) 1WPT but it reduced TLC significantly at 2 and 4 WPT, respectively in rate of (17.8% and 48.8%). This was accompanied by significant reduction of lymphocytes (31.7% and 57.9%) at 2 and 4 WPT, respectively. On other hand, it increased the neutrophils count in high statistical significance (25.6%, 87.6% and 287.4%) at 1, 2 and 4 WPT, respectively and reduced eosinophilia in a rate reached 40.2% without significant effects on basophils and monocytes. MZD caused

significant reduction in TLC (14.2% and 35.1%), in lymphocytes (18.2% and 42%) at 2 and 4 WPT and in esinophils (9% and 34.5%) but significant increase in neutrophils at 2 or 4 WPT (53.5% and 215.7%) (Table 2). In this study, *S. mansoni*-infected non-treated mice showed progressive degree of thrombocytopenia (as the platelet count decreased in response to time of infection in rate of (14.1%, 20.7% and 33.6%) at 8,9 and 11 WPI, respectively as compared to the non-infected non-treated control mice. Treatment of infected mice with PZQ and MZD caused significant increase in the platelet count at 2 or 4 WPT and the effect was higher for PZQ (31.9% and 72.1%) followed by MZD (25.5% and 50.4%) (Figure 1).

Table 2. Total and Differential Leucocytic counts in S. mansoni-infected mice under different treatments at different follow up periods.

Parameters /Group	WPT	Mice groups					
		MZD	PZQ	Infected Non-treated	Non-infected Non-treated		
Total Leucocytes (10 ³ cell//ul)	1	12.36±1.83 (+0.1)	11.00±1.84 (-10.8%)	12.34±2.50 (+20.7%)	10.22±1.91		
	2	11.90±1.70b (-14.2%)	11.40±0.78B (-17.8%)	13.87±0.70A (+46.9%)	9.44±1.29		
	4	9.17±2.15B (-35.1)	7.23±0.55B (-48.8%)	14.13±0.85A (+101.2%)	7.02±0.62		
Lymphocytes (%)	1	70.00±1.20 (-1.4%)	68.80±1.77b (-3%)	71.00±3.02a (+5.1%)	67.50±0.48		
	2	53.90±1.52B (-18.2%)	45.00±3.17B (-31.7%)	65.90±1.51A (+17%)	56.30±0.05		
	4	40.00±1.79B (-42%)	29.00±1.13B (-57.9%)	69.00±1.53A (+38.8%)	49.70±0.71		
Neutrophils (%)	1	21.20±1.46 (+10.9%)	24.00±1.58B (+25.6%)	19.10±1.98A (-24.5%)	25.30±1.98		
	2	38.70±1.90B (+53.5%)	47.30±3.61B (+87.6%)	25.20±1.15A (-33.3%)	37.80±0.39		
	4	50.20±1.04B (+215.7%)	61.60±9.50B (+287.4%)	15.90±1.74A (-62.1%)	42.00±0.49		
Esinophils (%)	1	7.10±0.65b (-10.1%)	7.10±0.11b (-10.1%)	7.90±0.45A (+51.9%)	5.20±0.37		
	2	6.00±0.32B (-9%)	5.60±0.25b (-15.1%)	6.60±0.68 (+83.3%)	3.60±0.28		
	4	9.10±0.08B (-34.5%)	8.30±0.35B (-40.2%)	13.90±0.14 (+90.4%)	7.30±0.31		
Monocytes (%)	1	1.30±0.09 (0%)	1.40±0.03 (-7.6%)	1.30±0.20 (0%)	1.30±0.61		
	2	1.90±0.07 (+5.5%)	1.80±0.26 (-5.2%)	1.90±0.03 (0%)	1.90±0.09		
	4	1.10±0.06 (0%)	1.10±0.01 (-9%)	1.10±0.11 (+10%)	1.00±0.07		
Basophils (%)	1	0.4±0.01 (-42.8%)	0.70±0.05 (-14.2%)	0.70±0.01 (0%)	0.70±0.01		
	2	0.30±0.02 (-42.8%)	0.30±0.01 (-25%)	0.40±0.01 (0%)	0.40±0.01		
	4	0.00±0.02 (0%)	0.00±0.00 (0%)	0.00±0.00 (0%)	0.00±0.00		

The statistical test used was independent two-sample t-test. Values were expressed as mean \pm SD. Numbers in parentheses indicate the percentage change. a: Statistically significant at P < 0.05 compared to non-infected. A: highly significant at P < 0.05 compared to non-treated. B: highly significant at P < 0.01 compared to non-treated.

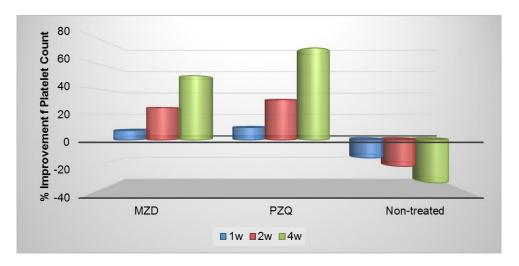


Fig. 1. Percentage change in mean Platelet counts in *S.mansoni*-infected mice under MZD and PZQ treatments at different follow up periods.

DISCUSSION

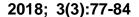
Schistosomes are blood flukes that inhabit the blood vessels of humans, *Schistosoma mansoni* and S. *japonicum* live in the mesenteric venules while S. *haematobium* adults live in the veins of the vesical plexus (Ross *et al.*, 2002). These parasites are exclusive blood feeders, and it is estimated that female S. *mansoni* worms can ingest approximately 330000 erythrocytes per hour and the ingested red cells are lysed in the gastrodermis to enable the parasites to digest hemoglobin (Don *et al.*, 2008). RBCs provide essential nutrients for the sexual maturation of female S. *japonicum* (Wang *et al.*, 2015).

In this study, the count of the erythrocytes in the blood of schistosomiasis-infected mice showed highly significant and progressive decrease in the number from the 8th week of infection till the 11th week to 30.8% associated with decrease in haemoglobin level to 59.4% as well as the haematocrit value (HCT) to 41.7% as compared to the nontreated mice. The erythrocytic indices were decreased such as MCV to 25%. MCH to 47.88% and MCHC to 30.33%. The decline in the Hb denoted evidence of anaemia as defined by the WHO as a decrease in haemoglobin less than 13 g/dl in men or 12 g/dl in women) (WHO, 2011) .Several works mostly in all schistosomes reported progressive decrease in the Hb. RBCs and HCT which indicate hypochromacia and as there was progressive decrease in MCV at the advance of infection especially at 11 WPI indicating microcytosis, so this type of anemia may direct the etiology to iron deficiency. This cause was reported previously in human (Friedman et al., 2005; Leenstra et al., 2006; Cappellini et al., 2015) or experimentally infected animals (Abdel-Ghaffar and

Qurtam, 2001; Soliman and El-Shenawy, 2003; Sewify, 2009; Butler et *al.*, 2012; Al-Kazzaz, 2014).

Treatment with PZQ resulted in progressive increase in the RBCs count (4%,16.9% and 12.9%), HB level (11.9%,57% and 107.6%), HCT% (12.5%,40.1% and 42.5%), red blood cell indices [MCV (3.2%,20% and 26.2%), MCH (7.3%,34.12% and 83.9%) at 1,2 and 4 WPT and MCHC(12% and 45.7%) at 2 and 4 WPT, respectively as compared to the infected non-treated mice. These findings indicate that PZQ had no damaging effect on erythrocytes and their indices in S.mansoni infected mice as previously reported (Ahmed, 1993). MZD resulted in significant improvement in these parameters in the 4th week of treatment and proved to be safe on erythrocytic parameters as previously reported by Massoud et al. (2000) who tested MZD in doses 50,100 and 200 mg/kg for 2 months to normal rats and reported non-significant changes on HB, HCT and RBCs counts. Improvement in HB level about 14% at 3 months after MZD treatment (in doses 15 mg/kg for 3 days) was noticed in 49 patients infected with intestinal schistosomiasis (Soliman et al., 2004; Waheeb and Abdel Hafeez, 2001).

Currently in this work, Leukocytes showed significant elevation in infected mice in a rate of 46.9% and 101.2% at 9 and 11 WPI respectively). This reported leukocytosis was nearly similar to the results previously reported (Soliman *et al.*, 2004; Freudenstien-Dan *et al.*, 2003; Allan *et al.*, 2014). Such increase in the total leukocytes counts was attributed to the stimulation of the cellular production as a powerful defense reaction against the schistosomes and/or their ova (Soliman and El-Shenawy, 2003). The activated leucocytes are known to participate in immunity to *S.mansoni*, where they attach to the parasite surface and secrete





schistosomicidal substances as cationic protiens, hydrolytic enzymes, and oxidants implicated in the damage of the schistosomes (Freudenstien-Dan *et al.*, 2003). Other studies reported leucopenia (low WBCs) in *S. mansoni*-infected mice at 8 WPI (Allam, 2009; Mahmoud and El-Bessoumy, 2013). However, Abdel-Mottaleb *et al.*, 2008 reported non-significant changes in the total leucocytic count in *S. mansoni*-infected mice at 11WPI.

In this work, infected non-treated group revealed progressive lymphocytosis in relation to the time of infection reaching 38.8% at 4 WPI. These results were in agreement with the results of Allan et al. (2014) and Soliman and El-Shenawy (2003) who reported lymphocytosis at 6 or 9 WPI but not agree with other reports where there was lymphopenia ranging from 20.2 to 59.2% at 8 or 11 WPI (Thabet et al., 2007; Allam, 2009; Abdel-Mottaleb et al., 2008; Mahmoud and El-Bessoumy, 2013). Neutropenia was evident in an ascending manner in response to infection in non-treated mice in a rate of (24%, 33.3% and 62.1%) at 8,9 and 11 WPI. Variable degrees of neutrophilia ranging from 16.4% to 231% in S. mansoni infected mice at 8,9 and 11 WPI were reported by others (Soliman and El-Shenawy, 2003; Thabet et al., 2007; Allam, 2009). On the contrary, others reported decreased rate of neutophils (38.1% and 59.5%), respectively in infected non-treated mice at 8 or 11 WPI (Mahmoud and El-Bessoumy, 2013; Abdel-Mottaleb et al., 2008).

In this study, Eosinophils flourished in non-treated infected mice in progress to infection time as there was increased rate of 51.9%, 83.3% and 90.4% at 8, 9 and 11 WPI. Eosinophilia was reported at 8 WPI in a rate of 238.4% and 158.3% respectively by Allam (2009) and Mahmoud and El-Bessoumy (2013). While, Soliman and El-Shenawy, 2003 observed 70% increase in the mean value of esinophils in infected non-treated animals at 9 WPI. Thabet *et al.*,2007; Abdel-Mottaleb *et al.*, 2008 reported 175.4% and 415.3% increase in the level of esinophilic count at 11 WPI, respectively.

The link between helminth infections and increase in the count of eosinophils in the blood and tissues of the host is well known (Reimert *et al.*, 2006). During the acute infections with tissue-migrating larvae or following the sudden release of antigens from parasites dying either spontaneously or following chemotherapy is characterized by helminth-induced eosinophilia (O'Connell and Nutman, 2015).

Monocytes and basophils were not significantly changed in infected non-treated mice at both 1,2 or 4 weeks post-infection as previously reported (Allam, 2009; Abdel-Mottaleb *et al.*, 2008) at 8 or 11 WPI. However, Soliman and El-Shenawy, 2003; Mahmoud and El-Bessoumy, 2013 reported monocytosis at 9 or 11 WPI.

Treatment of infected mice with PZQ resulted in nonsignificant decrease in WBCs count (10.8%) 1WPT but the drug reduced significantly TLC at 2 and 4 WPT, respectively in rate of (17.8% and 48.8%). This was accompanied by significant reduction of lymphocytes (31.7% and 57.9 %) at 2 and 4 WPT, respectively. Treatment with PZQ decreased leukocytosis significantly in a progressive manner from 10.8%,17.8 and 48.8% at 1, 2 and 4 WPT, respectively. On other hand, it increased the neutrophils count in high statistical significance (25.6%, 87.6% and 287.4 %) at 1, 2 and 4 WPT, respectively and reduced eosinophilia in a rate reached 40.2% and lymphocytosis to 57% at 4 WPT, respectively without significant effects on basophils and monocytes. MZD caused significant reduction in TLC (14.2% and 35.1%), in lymphocytes (18.2% and 42%) at 2 and 4 WPT and in esinophils (9% and 34.5%) but significant increase in neutrophils at 2 or 4 WPT (53.5% and 215.7%). Massoud et al. (2000) found non-significant change in total and differential leucocytic counts at 1,2,4 and 8 WPT with MZD in normal healthy rats orally in 3 dose levels 50,100 and 200 mg/kg for 2 months. Waheeb and Abdel Hafeez, 2001 reported non-significant change in WBCs count and esinophils 2 months after treatment with MZD (15 mg/kg for 3 days) in cases of intestinal schistosomiasis.

In the current study, S.mansoni-infected non-treated mice showed progressive degree of thrombocytopenia (as the platelet count decreased in response to time of infection in rate of (14.1%, 20.7% and 33.6%) at 8,9 and 11 WPI, respectively as compared to the non-infected non-treated control mice .These results agreed with those of Stanley et al.at 12 WPI and against what reported by El-Shenawy, 2008 who found significant thrombocytosis (+107.1%) at 7 WPI while Thabet et al. (2007) reported non-significant change in platelet count in S.mansoni-infected mice at 11WPI. Treatment with PZQ or MZD caused significant increase in the platelet count at 2 or 4 WPT and the effect was higher for PZQ (31.9% and 72.1%) followed by MZD (25.5% and 50.4%). This elevation in platelet counts may be due worm death and subsequently decrease in egg excretion depending on the potency of the drug.

CONCLUSION

This study declared that PZQ and MZD as antischistosomal drugs were highly safe without adverse haemtological effects on infected treated mice and PZQ showed more ameliorative effects than MZD.

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CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

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