World Journal of Clinical Pharmacology, Microbiology and Toxicology
World J. Clin. Pharmacol. Micrbiol. Toxicol Vol 2 [2] March 2016: 05-12
Online ISSN 2454-1729
Journal's URL: http://wjcpmt.com
Impact factor [JIF] : 1.05
Global Impact Factor: 0.384

ORIGINAL ARTICLE

Biochemical Studies on the effects of *Commiphoramolmol* extract (Mirazid) compared to Praziquantel in Experimental *Schistosomiasis mansoni*

Mohammad Aziz[1], Amer Ragheb Adel Aziz [2]
[1]Department of Parasitology,Medical Research Institute ,Alexandria University, Alexandria, Egypt.Safepharma Research Laboratory, Alexandria, Egypt.
[2]Department of Parasitology,Faculty of veterinary medicine, Souhag University, Souhag; Egypt, 82524.
Corresponding Author :Amer Ragheb Adel Aziz (amerrageb77@yahoo.com)

ABSTRACT
Schistosoma mansoni worms inhabit the portal triad which may affect the blood elements.To compare the ameliorative effects of Commiphora molmol extract (Mirazid,MZD) and Praziquantel (PZQ) on some biochemical parameters in S.mansoni-infected mice. Swiss albino mice (n=72) were used in this study and were divided into 4 equal groups of 18 mice each; G1; was normal non-infected non-treated control .G2-G4 were infected with 100 S.mansoni cercariae and classified into G2; non-treated infected control group given only the vehicle; G3 was infected and treated with MZD at a dose of 500 mg/kg for 5 days and G4 was infected and treated with PZQ in a dose of 500 mg/kg for 2 days. Treatment started 7 weeks post-infection by oral route. Blood samples were collected at 1, 2 and 4 week post treatment to obtain serum for liver functions (ALT, AST and ALP), kidney functions tests (blood urea and serum creatinine) and cholinergic function (serum cholinesterase level). PZQ ameliorated the activities of the serum enzymes alanine aminotransferase, aspartate aminotransferase and alkline phosphatase more than MZD compared to infected untreated groupas PZQ decreased significantly ALT at 1, 2 and 4 WPT as well as AST and ALP activity at 2 and 4 WPT whereas, MZD resulted in significant reduction in ALT activity at 1, 2 and 4 WPT as well as AST and ALP activity only at 2 and 4 WPT. PZQ caused progressive significant reduction in the elevated levels of urea and creatinine at 1, 2 and 4 WPT, respectively than the produced by MZD.PZQ and MZD caused significant elevation in the level of AChE, this effect was greater detected earlier for MZD, at 2 and 4 WPT for PZQ. PZQ and MZD were safe drugs without adverse biochemical effects on infected treated mice and PZQ showed more corrective action than MZD.
Key words: *acetylcholinesterase, biochemical, Commiphora molmol, kidney, liver, mice, mirazid, praziquantel, Schistosoma mansoni.*

CITATION OF THIS ARTICLE
Mohammad Aziz, Amer Ragheb Adel Aziz. Biochemical Studies on the effects of *Commiphoramolmol* extract (Mirazid) compared to Praziquantel in Experimental *Schistosomiasis mansoni. World J. Clin. Pharmacol. Microbiol.Toxicol. Vol 2 [2] March 2016: 05-12*

INTRODUCTION

Schistosomiasis is a standout amongst the most far reaching of the major parasitic illnesses and its negative financial and general wellbeing sway in tropical and subtropical locales of the world (WHO; and EEMRO, 2007). Horribleness because of *S. mansoni* disease is basically as an aftereffect of the host's reactions to schistosome egg antigens to frame granulomas for the most part in the digestion systems and the liver where the eggs are caught (Bindseli*et al*., 2004).At present, there is no antibody accessible, and Praziquantel (PZQ) is the chemotherapeutic specialist of decision with great viability against the grown-up worm of all schistosome species. Surely, it has successfully turned into the main hostile to schistosomal drug that is monetarily accessible everywhere throughout the world(Abdul-Ghani, et al., 2009). Mirazid (MZD) rose in Egypt since 2002 as another treatment of schistosomiasis as a characteristic determined pharmaceutical arrangement of myrrh or *Commiphora molmol.*

MATERIALS AND METHODS

Animals

Animals were housed in polycarbonate boxes with steel-wire tops (not more than six for each enclosure) and had relations with wood shavings. Surrounding temperature was controlled at 22 ± 30C with a relative stickiness of 50± 15% and a 12-h light/dull photoperiod. Food and water were provided ad libitum.

Drugs:

MZD and PZQ was bought from neighborhood advertise and were broken down in 4% Cremophor EL as a vehicle.

Exploratory outline and treatment regimens

Cercarial shedding:

Infected *B. alexandrina* snails were washed with dechlorinated water and kept in a circulated air through aquarium (utilizing an electric pump) in a dull spot (by covering the glass bath with a dark plastic pack). Before use, snails were washed delicately with a little volume of water to expel excrement and different flotsam and jetsam, then resuspended in water (1ml/snail) and left revealed in a glass test tube under white bright light for a time of 30–60min to discharge the cercariae. Tender shaking to guarantee homogenous dispersion of cercariae and 1ml of cercarial suspension was pipetted and set on glass slides; a drop of iodine was added to every slide to kill, stain and alter the cercariae. The quantity of cercariae was checked in every slide with the guide of a stereobinocular microscope.Generally, three counts were made 3ml cercarial suspension and the exact number per 1ml was ascertained Fawcett, and Scott. (1960).

Cercarialinfection of mice:

Mice were infected utilizing as per Smithers and Terry (1965). Every mouse was exposed independently to around 100 *S. mansoni* cercariae, and then infected mice were then isolated in an independent stainless steel wiremesh cages, and got a standard very much adjusted eating routine and water.The mice were housed in a room under controlled natural temperature. Stool examination was performed 50 days after cercarial infection to decide the shedding of eggs.

Drug administration:

At 7 weeks post infection(WPI), MZD was orally given to mice in a dosage 500 mg/kg for 5 days (0.1ml solution for each mouse).The measurement was chosen as indicated by Botros et al., (2004) and Massoud et al., (2004) which is four-fold the therapeutic dose in mice (125 mg/kg) based on Food and Drug Administration guidelines by converting the human dose to those for experimental animals. PZQ was given in a dose of 500 mg/kg for 2 days according to William *et al.*, (2003).

Biochemical studies:

Blood samples were collected in centrifuge tubes without anticoagulant and centrifuged at 3000 rpm for 20 min. Serum was stored at - 20^{o} C until used for biochemical assays using commercial kits. The liver function tests were assessed using alanine aminotransaminase (ALT), aspartate aminotransaminase (AST,Diasys diagnostics) according to Reitman and Frankel (1957) and alkaline phosphatase (ALP,Tecno diagnostics) according to Kind and King(1954).Blood urea and serum creatinine were used to assess kidney functions using urea and creatinine kits (Diamond Diagnostics) according to Fawcett and Scott (1960), the previous tested parameters were counted by photometer 5010 (fully-automated chemistry analyser, India). Cholinesterase (ChE) level was selected to assess the neurotoxic potential inmice blood using Spinreact chemistry analyser/Spinlab (Spain) according to the colorimetric method of Ellman*et al*., (1961).

Ethical considerations:

The study protocol was reviewed and approved by the Ethics Committee of the MRI, University of Alexandria.

Statistical analysis

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

$$\text{Change in infected (\%)} = \frac{\text{mean values in non-infected (c)} - \text{mean values in non-treated (t)}}{\text{mean values in non-infected (c)}} \times 100$$

$$\text{Change in treated (\%)} = \frac{\text{mean values in non-treated (c)} - \text{mean values in treated (t)}}{\text{mean values in non-treated (c)}} \times 100$$

RESULTS

In this work, mice in the infected non-treated group showed highly significant elevation of serum ALT (54.5%, 80.6% and 202.2%), AST (45.8%, 49.2% and 79.5%) and ALP levels (123.2%, 127.9% and 212.2%) compared

to non-infected normal mice at 8, 9 and 11 WPI. But under the effect of PZQ, the serum ALT decreased significantly 29.1%, 35.1% and 53.5% at 1, 2 and 4 weeks after treatment. PZQ also reduced AST (21.3% and 50.3%) and ALP activity (43.2% and 65.5%) at 2 and 4 WPT as in Table (1).Table (2) indicating the treatment of infected mice with PZQ or MZD caused progressive significant reduction in the elevated levels of urea (12.5%, 33.9% and 60.2%) for PZQ and (21.3%, 26.8% and 45.7%) for MZD at 1, 2 and 4 WPT, respectively, both drugs significantly reduced creatinine at 4 WPT.AChE activity in *S.mansoni*-infected mice 8 WPI with 100 cercariae showed progressive decrease with the time of infection as there was significant decrease 11.4% at 8WPI, and at 9 and 11 WPI. there was highly significant decrease in blood AChE activity 19.8% and 23.5%, respectively).Treatment of mice with PZQ and MZD caused significant elevation in the depressed level of AChE, This effect was greater detected earlier for MZD (10.3%, 16.2% and 25.4%).It was observed (22.5% and 31.8%) at 2 and 4 WPT for PZQ.

Table (1): Liver function testsin *S. mansoni*-infected mice treated with different drugs at different times.

Parameters	WPT	MZD	PZQ	Infected Non-treated	Non-infected Non-Treated
ALT (U/L)	1	49.25±4.66 (-23.5%) B	45.60±1.40 (-29.1%) B	64.40±3.90 (54.5%) A	41.37±6.21
	2	68.50±8.61 (-25.9%) B	60.00±6.56 (-35.1%) B	92.50±3.54 (80.6%) A	51.20±7.96
	4	60.00±6.79B (-40.1%)	53.75±6.27 B(-53.5%)	100.33±6.51 (202.2%) A	33.20±5.89
AST (U/L)	1	109.67±4.93 (-8.3%)	110.50±10.66 (-7.6%)	119.60±11.00 (45.8%) A	82.00±6.96
	2	130.00±12.7 b (-9.7%)	113.33±11.73 B (-21.3%)	144.00±7.13 (49.2%) A	96.50±7.92
	4	95.00±9.08 (-40.25%) B	79.00±4.85 (-50.3%) B	159.00±8.17 (79.52%) A	88.57±9.24
ALP (U/L)	1	89.00±6.24 (-20.6%)	78.50±26.41 (-30%)	112.20±37.60 (123.2%) A	50.25±17.71
	2	118.50±8.33 B (-32.2%)	99.33±4.16 (-43.2%) B	175.00±9.40 (127.9%) A	76.77±2.01
	4	78.67±3.32 (-49.3%) B	53.50±4.57 (-65.5%) B	155.33±6.01 (212.2%) A	49.75±2.41

a: *Statistically significant at P value < 0.05 compared to non-infected.****A :*** *Statistically highly significant at P value < 0.01 compared to non-infected.* ***b :*** *Statistically significant at P value < 0.05 compared to non-treated ,* ***B:*** *Statistically highly significant at P value < 0.01 compared to non-treated.*

Figure (1): Liver function testsin *S. mansoni*-infected mice treated with different drugs at different times.

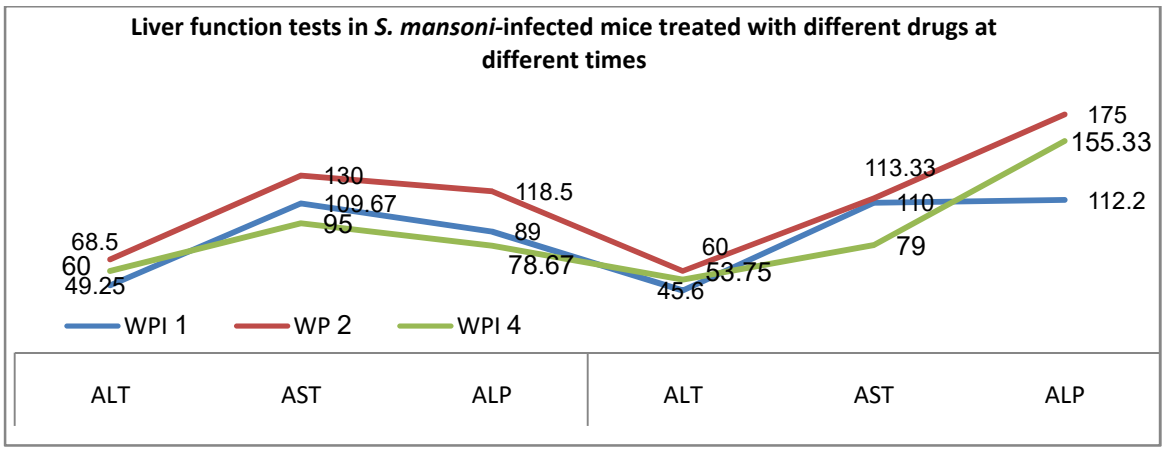

Table (2): Kidney function tests in*S.mansoni*-infected mice under different treatments at different follow up periods.

Parameters	WPT	MZD	PZQ	Infected Non-treated	Non-infected Non-treated
Blood Urea (mg/dl)	1	31.45±2.58 B(-21.3%)	35.00±2.60 B (-12.5%)	40.00±2.92 A (+61.2%)	24.80±1.74
	2	40.25±3.89 B (-26.8%)	36.33±6.03 B (-33.9%)	55.00±4.14 A (+88.3%)	29.20±2.66
	4	40.00±3.00 B (-45.7%)	29.25±3.30 B(-60.2%)	73.67±7.75 A (+255.3%)	20.73±3.84
Serum Creatinine (mg/dl)	1	1.28±0.09 (+20.7%)	0.78±0.31 (-26.4%)	1.06±0.30 (+17.7%)	0.9±0.44
	2	1.18±0.08 (-5.6%)	0.90±0.36 (-28%)	1.25±0.09 (+78.5%) a	0.70±0.43
	4	0.90±0.01 b (-33.1%)	0.75±0.24 b (-48.2%)	1.45±0.54 A (+150%)	0.58±0.17

*Values were expressed as mean ± SD, Numbers in parentheses indicate the percentage change.**a:** Statistically significant at P value < 0.05 compared to non-infected.**A :** Statistically highly significant at P value < 0.01 compared to non-infected. **b :** Statistically significant at P value < 0.05 compared to non-treated , **B:** Statistically highly significant at P value < 0.01 compared to non-treated.*

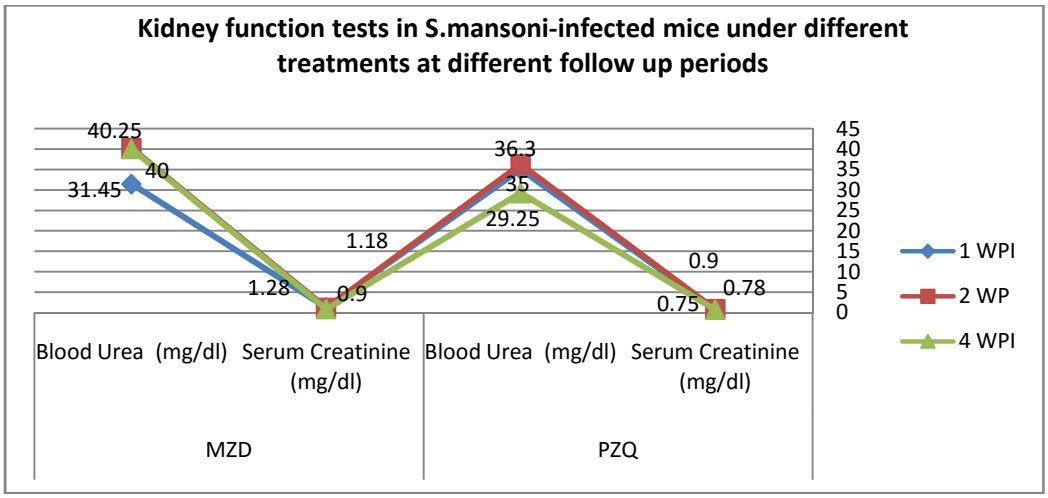

Figure (2): Kidney function tests in*S.mansoni*-infected mice under different treatments at different follow up periods.

Table (3):Theblood acetylcholinesterase (AChE) levelin *S. mansoni*-infected mice treated with Mirazid or Praziquantel 1,2 and 4 weeks post-treatment compared to non-treated and non-infected mice.

WPT	MZD	PZQ	Non-treated	Non-Infected
1	9.91±1.5b (+10.3%)	9.32±0.19 (+3.5%)	9.00±0.8 a (-11.3%)	10.15±0.65
2	9.30±0.40B (+16.2%)	9.80±0.40B (+22.5%)	8.00±0.17A (-19.8%)	9.98±0.48
4	9.50±0.92B (+25.4%)	9.98±0.15B (+31.8%)	7.57±0.66 A (-23.5%)	9.90±0.40

*Values were expressed as mean ± SD, Numbers in parentheses indicate the percentage change.**a:** Statistically significant at P value < 0.05 compared to non-infected.**A :** Statistically highly significant at P value < 0.01 compared to non-infected. **b :** Statistically significant at P value < 0.05 compared to non-treated , **B:** Statistically highly significant at P value < 0.01 compared to non-treated.*

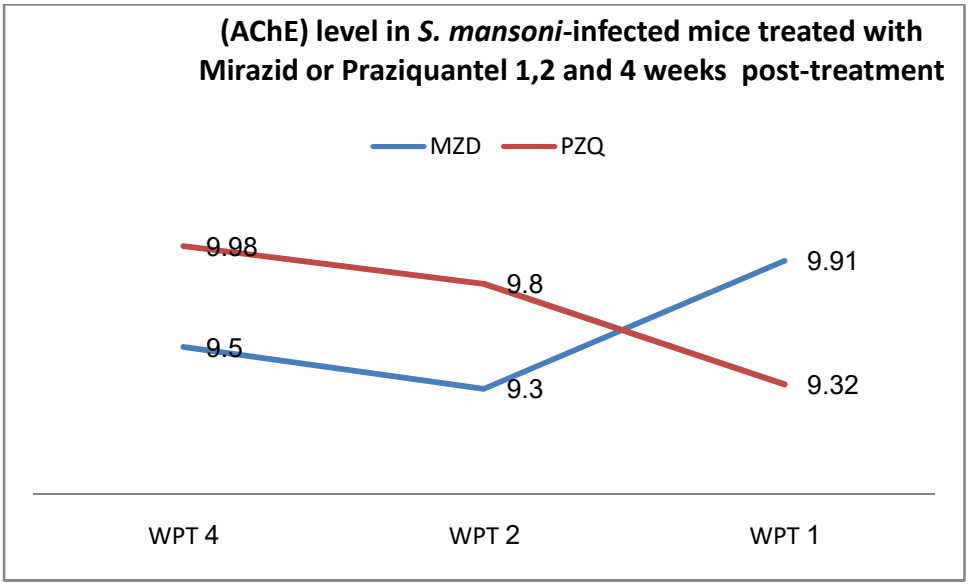

Fig.3.blood acetylcholinesterase levelin *S.mansoni*-infected mice under different treatments at different periods of follow up.

DISCUSSION

Liver harm can be recognized by measuring the adjustments in liver compounds (ALT, AST and ALP) levels contrasted with the control. Where its hepatocytes show contrasts in the confinement and centralization of some enzymatic frameworks. These enzymes served as markers for various cell organelles and any imperfection of them will be reflected to the catalyst movement itself (Ammar et al., 2009; and Meera *et al.,* 2009).ALT is a liver particular chemical just essentially raised in hepatobiliary sicknesses. Increment in AST level can happen regarding harms of heart or skeletal muscle and also liver parenchyma. ALP is of enthusiasm for the analysis of hepatobiliary issue and bone infections. Parallel estimation of ALT, AST and ALP is in this way connected to recognize liver from heart or skeletal muscle damages.So considering changes in these enzymatic levels could be useful in assessing the harming impacts of *S.mansoni* infection on the liver of the host and assessing the conceivable reactions of various medicines and the change happening in such enzymes after medications, Burtis A., and Tietz. (1999).

Botros et al.,(2007) discovered 112.1% elevation in ALT level in *S.mansoni*-infected mice at 8 WPI .El-Lakkany et al.,(2012) reported 80% increase in serum ALT at 9 WPI, Saba-El Rigal and Hetta (2006) discovered 238.9% and 119.3% rise in the serum AST and ALP levels separately at 8 WPI.Abdel-Mottaleb et al., (2008) discovered 88% increment in serum ALP at 11 WPI. El-Shenawy et al. (2008) and Mahmoud et al., (2002) credited the increased liver enzyme level to the hepatic cell harm and expanded cell film porousness or to substantial Schistosoma egg deposition. Awadalla et al., (1975),and El-Aasar et al., (1989) ascribed the elevation in enzymatic activities to the bothering of the liver cells by poisons or metabolic products of developing schistosomules, grown-up worms and eggs or to expanded loss of intracellular enzymesby dispersion through cell membranes which seems to go about as a jolt to the blend of more enzymes. Higher rates of formation would, thusly, expand the rate of dispersion and henceforth elevate serum activities. this was consistent with the discoveries of Botros et al., (2007) who discovered 33.2% and 43.3% diminishment in ALT level in PZQ-treated mice at 1 or 2 WPT (500 mg/kg for 2 days at 6 WPI). Notwithstanding, Sewify (2009), and El-Lakkany et al., (2012) discovered immaterial change in the AST level at 2 WPT in PZQ-treated mice. MZD treatment of infected mice brought about critical changes in the action of liver enzymes. This was showed by critical diminishment in ALT movement at 1, 2 and 4 WPT (23.5%, 25.9% and 40.1%). The huge diminishment in serum AST and ALP levels happened just at 2 WPT (9.7% and 32.2%) and at 4 WPT (40.25%, and 49.3%). Massoud et al., (2000) reported non-noteworthy change in serum liver chemicals in solid rats orally given MZD dosages extending from 50-200 mg/kg for 2 months at 1, and 2 or 4 WPT. Saba-El Rigal and Hetta (2006) utilized MZD as a part of dosage of 600 mg/kg for 3 days in *S.mansoni*-infected mice (100 cercariae at 8 WPI). The level of ALT and AST was diminished 48.5% and 52.7%, separately at 3 WPT contrasted with the non-treated mice. Omar et al., (2005) concentrated on the impact of MZD 500 mg/kg or PZQ 1500 mg/kg day by day for 6 weeks on normal rats. There was non-noteworthy increase in the mean estimation of ALT in MZD-regarded rats when contrasted with the ordinary non-treated control; while PZQ instigated high elevation in the mean estimation of ALT contrasted with MZD. Likewise, PZQ prompted high increase in the mean estimation of AST level contrasted with MZD. Nephropathay or

nephrotic disorder was accounted for in human and exprimental animals infected with *S. mansoni*. The malady is accounted for to advance to end stage renal failure (Barsoum (2004), and Junior et al., 2013). Schistosomal nephropathy is most likely produced by chronic deposition of circulating immune complexes, antischistosome antibodies and schistosome antigens (Moriearty, and Brito (1977).Blood urea and serum creatinine are routinely utilized as biomarkers for appraisal of renal capacities. Urea is the last consequence of protiens metabolism; it is framed in the liver from their destruction. High level of urea can show up in the blood (uremia); in diet with abundance of protiens, renal maladies, heart disappointment, gastrointestinalhemorrhage. Creatinine is the consequence of the corruption of creatine (part of muscles), it can be changed into ATP, that is a wellspring of high vitality for cells. The creatinine generation relies on upon the alteration of the muscle mass, and it fluctuates little and the levels for the most part are extremely steady. Creatinine is discharged by the kidneys. With dynamic renal deficiency, there is maintenance in blood urea and raised creatinine level (Barsoum et al., 2013). In this study, the blood urea and serum creatinine in *S.mansoni*-infected mice was elevated because of the period of disease as they were progressively raised. EL-Shenawy et al., (2008) had reported almost comparative results as the blood urea and serum creatinine of mice infected by *S.mansoni*, demonstrated that huge increment (300% and 166.6%) individually when contrasted with non-contaminated mice at 7 WPI (100 cercariae).Sheir et al., (2001) and Massoud et al., (2000) reported that MZD was of no harm on kidney functions of normal healthy rats (orally given 50,100 and 200 mg/kg for two months) or healthy volunteers (10 mg/kg for 3 days following 2 months) and in addition infected treated patients. increase or decrease of the blood AChE will bring changes in the concentration of acetylcholine as when the enzyme is restrained, acetylcholine then gathered prompting toxicity showed by nicotinic, muscarinic or focal signs and indications as per the level of inhibition and therefore the receptors influenced, Giacobini (2004); Ballard et al., (2005); Schetinger et al., (2000); Kawashima , and Fujii, (2003); Lassiter et al.,(2003); Santarpia et al., (2013).Almost like the outcomes got by Sewify (2009), Saba El-rigal and Hetta (2006); who discovered 14% and 56.1% inhibition in serum cholinesterase (SCE) level in *S.mansoni*-infected mice at 7 or 8 WPI (with 100 cercariae either by paddling procedure or tail immersion technique), individually. The later said that the low SCE level is ascribed to low serum total proteins. AChE activity in *S.mansoni*-infected mice 8 WPI with 100 cercariae indicated dynamic reduction with the season of infection as there was noteworthy lessening 11.4% at 8WPI, and at 9 and 11 WPI. there was very noteworthy lessening in blood AChE level 19.8% and 23.5%, individually), which might be expected hepatocellular damage and thusly low serum protiens or may emission of toxins by the grown-up schistosomes hindering the enzyme activity. Badria et al.(2001) expressed that MZD in a measurements of 500 mg/kg for 3 days for S.mansoni-infected mice brought about death of adult worms ;might be because of loss of musculature (paralysis) . Hassan et al. (2003), and Sharaf (2004);examined the muscle tension of *S.mansoni* worms under the effect of MZD in rising concentrations 100,200,300 and 400 µg/ml .The drug elicited somatic muscle contraction and reached highest response with the higher concentration. It was found that exposure of isolated rabbit duodenum to MZD 150-300 µg/ml induced inhibitory effect on motility. However, it failed to evoke the contractile effect of acetylcholine (2µg/ml), so MZD is devoid of an effect on the muscarinic receptors.Saba-El rigal and Hetta (2006) found that MZD proved to have highly significant stimulatory activity on SCE level (14%) in normal mice.

Conclusion:This study declared that PZQ and MZD were highly safe without adverse haemtological or biochemical effects on infected treated mice with the advandage of more ameliorative effects in PZQ in comparsion to MZD.Schistosomiasis is associated with many complications; the most important of these are liver damage (WHO, 2010).Among the five different schistosome species, *Schistosoma mansoni* is the most abundant one in Egypt (Helmy et al.,2009). Pathology associated with *S. mansoni* results primarily from the accumulation of parasite eggs, giving rise to hepatomegaly that may be superseded by extensive liver fibrosis (Gryseels et al., 2006). It has also been shown that the granulomatous inflammatory response to *S. mansoni* eggs entrapped in the liver induces oxidative stress.

ACKNOWLEDGMENTS

Authors wish to express their thanks to all staff members of department of Parasitology, Medical Research Institute ,Alexandria University, Safepharma Research Laboratory and department of Parasitology,Faculty of veterinary medicine, Souhag University for their sincere cooperation during the study.

AUTHORS CONTRIBUTIONS

Mohammed Aziz and Amer R. Abdel Aziz worked in this study from preparation of animals under study, and drugs, and the sharing in the design of the experiment, biochemical studies, biostatistical analysis till

reading the results, and prepared the final manuscript, both authors read and approved the final version of the manuscript.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests, and Compliance with Ethical Standards, and research involving animals' participants.

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CONFLICT OF INTEREST	: Nil
Received	: 12.02.2016
Accepted	: 09.03.2016