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Berberine Protects Against *Schistosoma mansoni*-Induced Oxidative Damage in Renal and Testicular Tissues of Mice

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Abstract.- A complex interplay between schistosomiasis and function of different organs leads to the impairment of these organs. In this study, we demonstrated the protective effect of berberine chloride (BER) in schistosomiasis-inducted oxidative stress on renal and testicular tissues of mice compared to praziquantel (PZQ). Lipid peroxidation (LPO), nitric oxide (NO), glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR) were estimated. In addition, histopathology of kidney and testes in infected mice were elucidated. The results showed that BER normalized the concentration of GSH and the activities of SOD, CAT, GPx and GR, which were changed by infection and lowered the LPO level that were increased in infected mice. Moreover, BER was able to lower the NO level, while PZQ-treatment induced more elevation of this product. The protection by BER was extending to improve the histopathology of kidney and testes of infected mice. In conclusion, data presented here demonstrated that BER is a novel protective agent and these results indicated that BER could be useful in treatment of *S. mansoni* infection induced renal and testicular oxidative damage.

Keywords: *Schistosoma mansoni,* Berberine, Praziquantel, oxidative stress, antioxidant.

INTRODUCTION

Schistosoma spp., blood flukes, are parasitic helminths found mainly in developing countries with a tropical or subtropical climate and affects 200 million people worldwide. *Schistosoma mansoni*, *japonicum* and *mekongi* harbor in veins of the portal system and lay eggs in the blood vessels. The deposition of numerous eggs in the intestines and liver result in intestinal and hepatic granulomatous lesions, fibrosis, portal hypertension, and hepatosplenomegaly (Osada and Kanazawa, 2011). In contrast, *S. haematobium* mainly harbors in the venous plexus of the bladder and/or rectal venous plexus. This worm usually causes bloody urine and it is also considered to have an etiological relationship with bladder cancer (Vennervald and Polman, 2009). Because of the extensive distribution of schistosomes and morbidity due to egg deposition, researchers have been interested in the influences of schistosome infections on concomitant diseases (Osada and Kanazawa, 2011).

There is yet no vaccine available and the current mainstay of control is chemotherapy with praziquantel (PZQ). In view of concern about the development of tolerance and/or resistance to PZQ, there is a need for research and development of novel drugs for the prevention and cure of schistosomiasis (Wilson *et al*., 2008). Moreover, PZQ induces considerable adverse clinical effects, although several side effects occur within 24 hours, the mechanism of side effects of short-term treatment with PZQ has not been clarified(Pinlaor *et al*., 2008). Side effects due to PZQ usually occur in a relatively larger population of patients (30-60%) but they are mild and transient and disappear within 24 h. Dizziness, bloody or mucoid diarrhoea and abdominal pain are most frequently encountered following the treatment with PZQ. On the other hand, uncommon side effects such as joint pains, joint swellings, and myalgia and peri-tibial/ankle oedema are observed following treatment with PZQ (Mekonnen *et al*., 2013).

The association between *S. mansoni* infection and kidney lesions was investigated (Johansen *et al*., 1994). Chronic infection with *S. mansoni* is associated with glomerular disease in 10 to 15 percent of patients (Nussenzveig *et al*., 2002). In addition, testicular schistosomiasis caused by *S. mansoni* is exceedingly rare (Lopes *et al*., 2007). However, schistosomiasis has an important metabolic effect on testicular lipids as well as on the serum level of testosterone (Marzouki and Amin, 1997).

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Berberine (BER) is an isoquinoline alkaloid of the protoberberine type, with a long history of medicinal use in traditional eastern medicine. It is found in the root, rhizome, and stem bark of many plant species such as *Coptis chinensis*. BER extracts and decoctions have significant antimicrobial activities. Recent pharmacological studies have shown that BER also possesses antitumor, anti-HIV, antifungal, cardioprotective, immunoregulative, antimalarial, anti-inflammatory, antioxidative, anxiolytic, and analgesic effects (Abd El-Wahab *et al*., 2013; Al-Quraishy *et al.,* 2014; Othman *et al.,* 2014). BER is generally administered as a chloride or sulfate for clinical applications.

In the work presented here we examined the protective effect of BER on schistosomiasis-inducted oxidative stress and damage on kidney and testes of mice.

MATERIALS AND METHODS

Animals

Forty eight CD-1 Swiss male albino mice, weighing 20-25 g were provided by the Schistosome Biology Supply Center (SBSC) of the Theodor Bilharz Research Institute (TBRI), Giza, Egypt. The mice were maintained on a standard commercial pelleted diet in an air-conditioned animal house at 22-25°C. The animal experiments were conducted at the TBRI animal unit in accordance with international, ethical guidelines after approval of the institutional ethical committee of TBRI. Animals were bred under specified pathogen-free conditions and fed a standard diet and water *ad libitum*. The experiments were performed only with male mice at an age of 9-11 weeks and were approved by state authorities and followed Egyptian rules for animal protection.

Infection of mice

Schistosoma mansoni cercariae were obtained from Schistosome Biological Supply Center at TBRI. Mice were exposed to *S. mansoni* (70±5 cercariae/mouse) using tail immersion method modified by Oliver and Stirewalt (1952).

Experimental design

Animals were allocated to six groups of eight mice each. Group I served as vehicle control and received water (100 µl water/mouse) by oral administration for 10 days. Group II was treated with PZQ at 500mg/kg body weight (bwt) via 70% glycerine on two successive days. Group III was orally gaveged with 100 µl of 12 mg/kg bwt BER (one-third of the 50% lethal dose) (Sigma, St. Louis, MO, USA) (Jahnke *et al*., 2006) for 10 days. Group IV, Group V and Group VI were infected with *S. mansoni*. On day 46 post-infection with *S. mansoni*, the animals of Group V received PZQ and Group VI received BER by orally gavage at the same described doses of Groups II and III, respectively. On day 55 post-infection with *S. mansoni*, the animals of all groups were cervically dislocated. Kidney and testes were weighed and homogenized immediately to give 50% (w/v) homogenate in ice-cold medium containing 50 mM Tris–HCl, pH 7.4. The homogenate was centrifuged at 3000 rpm for 10 min at 4°C. The supernatant (10%) was used for the various biochemical determinations.

Histology of kidney and testes

Tissue samples of the kidney and testes of all groups were immediately fixed after animal dissection in 10% neutral buffered formalin. After 24 hours, samples were dehydrated and processed for paraffin sectioning. Then, routine Hematoxylin and Eosin (H&E) stains were performed on deparaffinized 3µm sections.

Biochemical analysis

Oxidative stress

Hydrogen peroxide contents of kidney and testes homogenates were determined according to the method of Fossati *et al*. (1980). Briefly, chromophore produced by chemical reaction of H_2O_2 of homogenate with 3,5-dichloro-2-hydroxy-benzensulfonic acid (DHBS) and 4-aminophenazone (AAP) in the presence of peroxidase was determined spectrophotometrically at 510 nm. The homogenates were also used to determine lipid peroxidation (LPO) by reaction of thiobarbituric acid (TBA), nitrite/nitrate (nitric oxide; NO) and glutathione.

Enzymatic antioxidant status

Homogenates of kidney and testes were used in determination of superoxide dismutase (SOD),

catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GR) activities.

Estimation of serum testosterone hormone

Quantitative measurement of serum testosterone was carried out adopting ELISA technique using kits specific for mice purchased from BioVendor (Gunma, Japan) according to the protocol provided with kit.

Statistical analysis

Results were expressed as the mean ± standard error of the mean (SEM). One-way ANOVA was carried out, and the statistical comparisons among the groups were performed with Duncan's test using a statistical package program (SPSS version 17.0). All p values are two-tailed and $p<0.05$ was considered as significant for all statistical analysis in this study.

RESULTS

Figure 1 shows the effect of PZQ and BER treatment on mice infected with *S. mansoni* for 55 days. The data demonstrates that, there was a significant increased in H_2O_2 contents (Fig. 1A), LPO content (Fig. 1B), in infected renal and testicular homogenates compared to the control group. Significant amelioration in H_2O_2 was detected in all infected-treated groups with PZQ and BER. Moreover, H_2O_2 and LPO contents in kidney and testes were returned to the control values after treatment with PZQ or BER.

NO contents in renal and testesticular homogenates increased significantly post 55 days of infection with *S. mansoni* compared to non-infected mice (Fig. 1C). Moreover, in both renal and testesticular homogenates, the content of NO in the PZQ-treated group was higher than that in the control group (P <0.05). However, PZQ treatment in infected mice caused significant increase in NO content in both renal and testicular homogenates compared to control group. The treatment with BER caused significant decrease in NO contents in both renal and testicular homogenates compared to infected group. Moreover, NO content in testicular homogenates were returned to control value.

Schistosomiasis in mice causes overproduction of cellular oxidants and modulation of antioxidant defense system. As observed during the study, *S. mansoni* infection led to modulation of several parameters of oxidative stress relative to control animals. After 55 days of infection with *S. mansoni*, GSH content, SOD and CAT activities in the renal and testicular homogenates decreased significantly compared to the controls (Fig. 1D-F). Moreover, PZQ treatment alone caused a significant decrease in GSH content in both renal and testicular homogenates. On the other hand; PZQ and BER elevated the content of GSH and the activities of SOD and CAT significantly compared to infected group. However, BER treatment returned GSH, SOD and CAT on renal and testicular homogenates to the control values (Fig. 1D-F).

Results listed in the Table I showed the effect of PZQ and BER on some antioxidant enzymes, namely GPx and GR. The data demonstrated that, there was a significant inhibition in GPx and GR activities in both renal and testicular homogenates of infected mice. On the other hand, a significant amelioration was detected in infected mice treated with PZQ and BER, however, the amelioration in BER treated group was better than that of PZQ treated group.

To elucidate organ injuries, kidney and testes histology were examined 55 days after schistosomiasis insult. Figure 2A showed that no pathological changes in the kidney samples were found in control. Renal tubules degeneration and necrosis and inflammatory cell infiltration were prominent in the kidney of infected group (Fig. 2D). In contrast, BER or PZQ post-treatment significantly attenuated these pathological changes induced by schistosomiasis (Fig. 2E, 2F).

Testicular histopathological examination demonstrated that schistosomiasis caused seminiferous tubules injury as manifested by tubular degeneration and vacuolization after schistosomiasis induction (Fig. 3D), which were significantly alleviated by BER and PZQ post-treatment (Fig. 3E, F). The similar findings were observed with regard to plasma levels of testosterone. Schistosomiasis caused a marked decrease in plasma testosterone levels in the infected group after 55 days. The decreased levels of testosterone were markedly elevated by BER post-treatment in *S. mansoni*-challenged mice (Fig. 4).

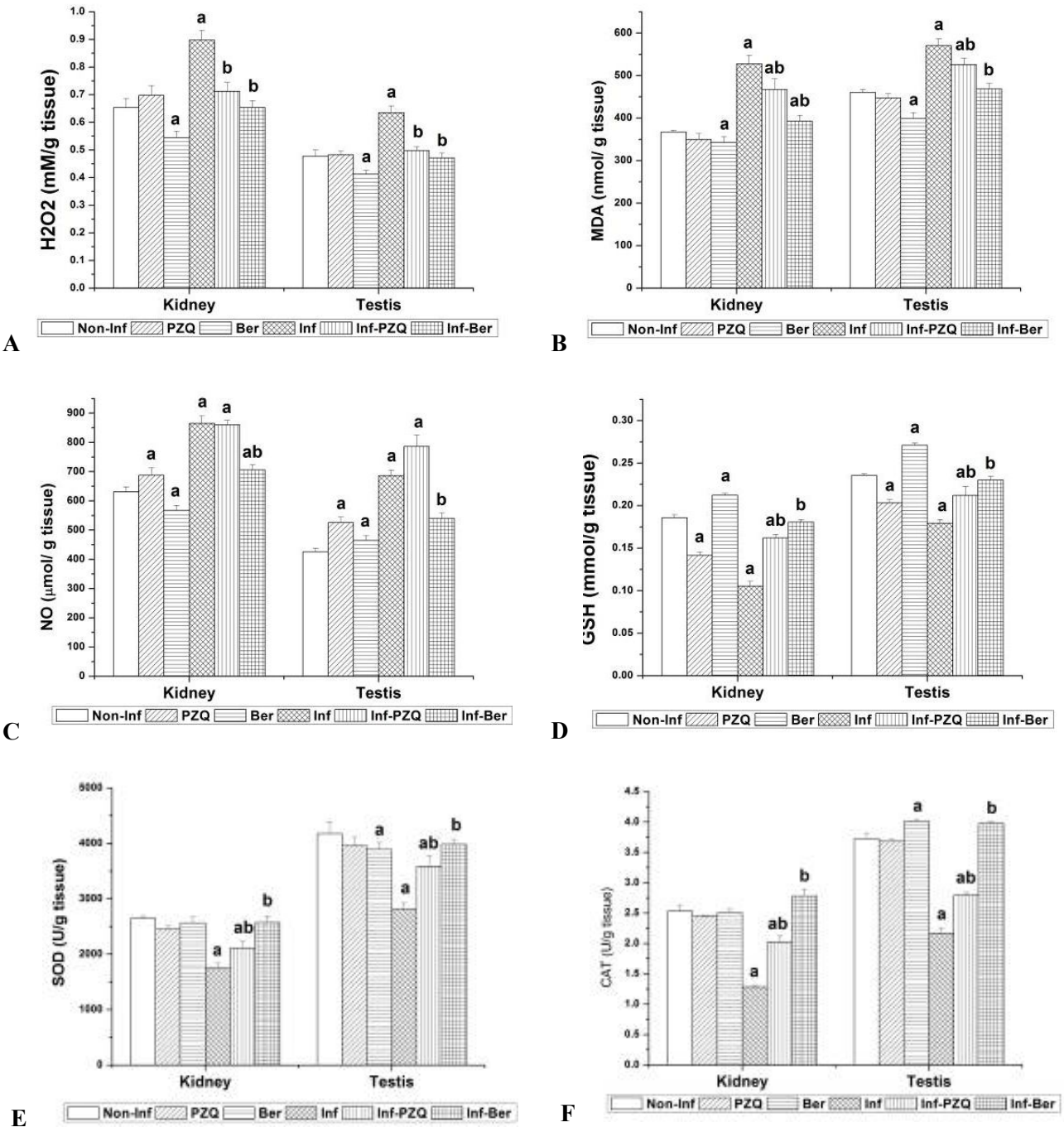

Fig. 1. Effect of berberine and PZQ on hydrogen peroxide levels (A), lipid peroxidation level expressed as malondiladehyde (MDA) equivalents formed (B), nitric oxide (NO) levels (C), glutathione (GSH) levels (D), superoxide dismutase (SOD) (E) and catalase (CAT) activities (F) in renal and testesticular homogenates of *S. mansoni* infected mice.

Data are presented as means ± SEM. a, significant change at $p<0.05$ with respect to non-infected group as a negative control group; b, significant change at $p<0.05$ with respect to Infected group as a positive control group.

Table I.- Effect of berberine and PZQ on some antioxidant enzymes, GPx and GR, activities in renal and testesticular homogenates of *S. mansoni* infected mice.

Groups	GPx (U/g tissue)		GR (µmol/g tissue)	
	Renal tissue	Testesticular tissue	Renal tissue	Testesticular tissue
Non-infected group	1572.7±15.30	1435.4±11.62	16.52±0.89	18.34±1.03
PZQ group	1454.6±11.64	1403.5±7.53	15.64±1.02	17.89±0.95
Berberine group	1647.5±9.47	1527.6±9.81[a]	17.31±0.95	19.89±1.14[a]
Infected group	987.4±7.57[a]	1038.9±8.51[a]	11.20±0.64[a]	12.64±0.57[a]
Infected-PZQ group	1689.2±13.74[b]	1506.3±12.36[b]	13.62±0.76[ab]	14.56±0.83[ab]
Infected-berberine group	1724.3±12.82[ab]	1621.4±14.27[ab]	15.04±0.53[ab]	17.94±1.06[b]

Data are presented as mean ± SEM
a, significant change at $p<0.05$ with respect to **Non-infected** group as a negative control group; b, significant change at $p<0.05$ with respect to **Infected** group as a positive control group.

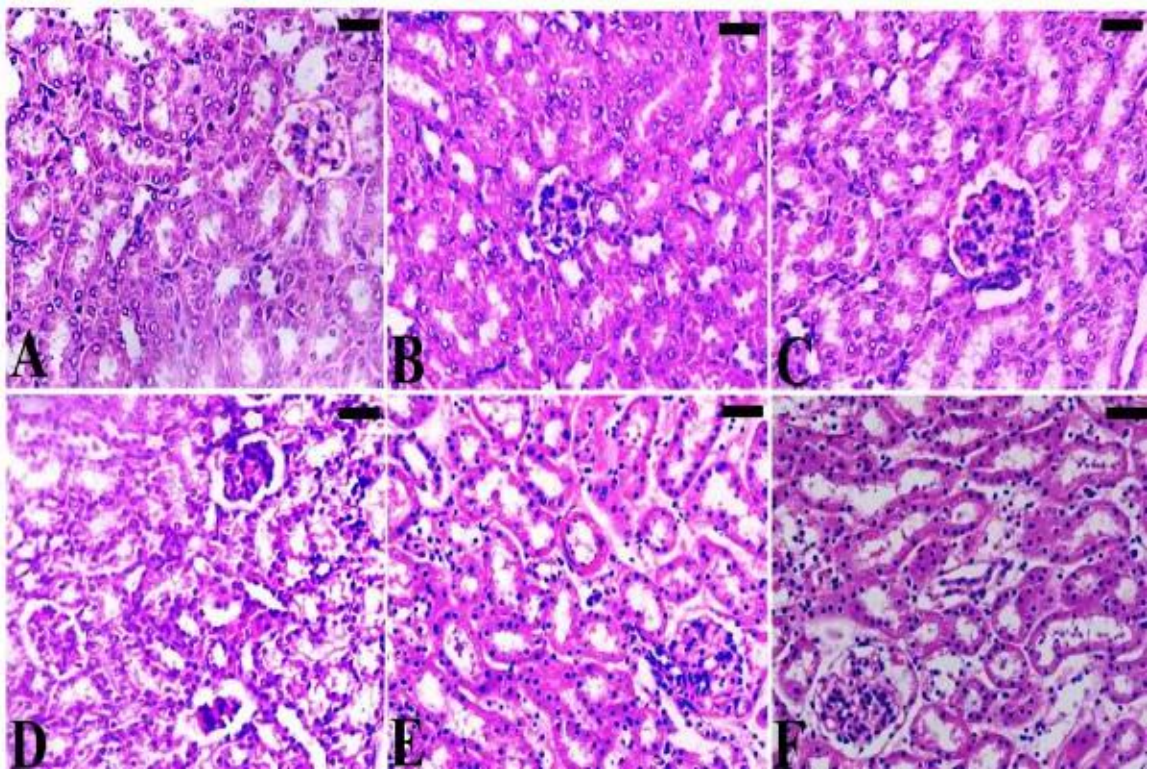

Fig. 2. Sections of mouse kidney infected with *S. mansoni* on day 55 *p.i.* (A) Non-infected kidney with normal architecture. (B) Non-infected, PQZ treated mouse kidney with normal structure. (C) Non-infected, berberine treated mouse kidney with normal structure. (D) Infected kidney with shrunken glomeruli and vacuolated tubules. (E) Infected PQZ treated kidney with less lesion. (F) Infected berberine treated mouse with improved tissue damage. Sections are stained with hematoxylin and eosin. Bar=50 µm.

DISCUSSION

The data obtained in the present study showed that, LPO was elevated in the kidney and testes of mice infected with *S. mansoni*. Since the complex mechanism of LPO is known to require the participation of highly reactive oxygen and other reactive metabolites in the chain of biochemical reaction, thus, in any part of the body where these free radicals are produced, lipid peroxides are in

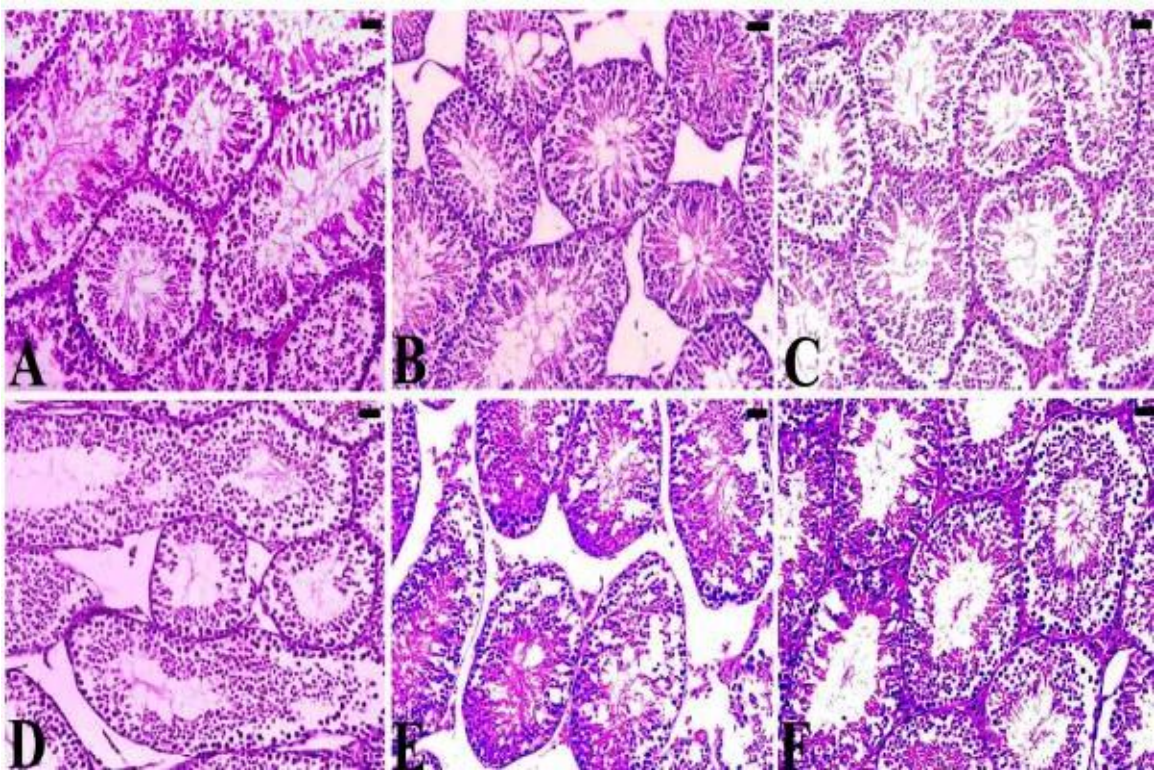

Fig. 3. Sections of mouse testes infected with *S. mansoni* on day 55 *p.i.* (A) Non-infected testes with normal architecture. (B) Non-infected, PQZ treated mouse testes with normal structure. (C) Non-infected, berberine treated mouse testes with normal structure. (D) Infected testes with seminefrous tubules injury. (E) Infected PQZ treated testes with less lesion. (F) Infected berberine treated mouse with improved tissue damage. Sections are stained with hematoxylin and eosin. Bar=50 μm.

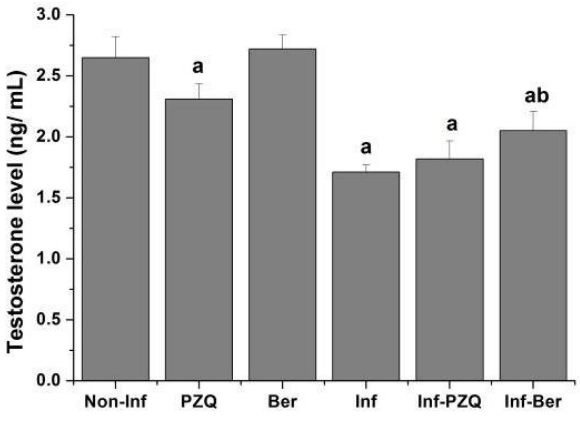

Fig. 4. *S. mansoni* induced changes in plasma testosterone level of mice.
Data are presented as Means ± SEM. a, significant change at $p<0.05$ with respect to Non-infected group as a negative control group; b, significant change at $p<0.05$ with respect to Infected group as a positive control group.

turn increased. Such phenomenon was previously reported by Shaheen *et al*. (1994) Moreover, several authors reported that oxidative stress due to schistosomiasis causes an elevation in LPO (Botros *et al*., 2007; Lores Arnaiz *et al*., 1995).

Results of GSH contents in the infected kidney and testes revealed a significant reduction resulting from an oxidative stress due to schistosomiasis (Lores Arnaiz *et al*., 1995). Such depletion may be caused by increased cytotoxicity with H_2O_2 which leads to inhibition in GR, the latter responsible for keeping GSH in its reduced state. An interesting finding which coincides with the present data was shown by Yegen *et al*. (1990) that reduction of cellular GSH is accompanied by increased LPO. BER brought the increased LPO level in schistosomiasis kidney and testes back to near the control one, which suggests that the protective effect of BER on these organs is

attributable to its defensive action on LPO damage. The altered enzymes activities and LPO in kidney and testes of schistosomiasis mice treated with BER indicate the protective effect on these organs. These findings suggest that BER had defensive nature of oxidative damage of cellular membranes and changes in the structural and functional integrity of subcellular organelles(Zhou *et al*., 2009).

Short-term PZQ treatment increased inducible nitric oxide synthase (iNOS) expression in the bile duct epithelium and inflammatory cells, which is supported by an increase in cellular levels of nitrate, end products of NO. Immediately after NO is produced, it rapidly reacts with superoxide anion (O_2^-) to form highly reactive peroxynitrite ($ONOO^-$), which mediates nitrative and oxidative damage to cellular components(Pinlaor *et al*., 2008). Such events were protected by the oral administration of BER and performed by using hematoxylin and eosin staining.

Activities of antioxidant enzymes (SOD, CAT, GPx and GR) were decreased significantly in infected mice, these reduction in activities probably because eosinophils and mast cells are accumulated in a short time and generate $O_2^{\cdot-}$ and H_2O_2, which play an important role in induction of host defense against parasite infection (McCormick *et al*., 1994). These finding were also showed in Inf-PZQ group, where the overproduction of ROS after short-term praziquantel treatment is supported by the increased level of LPO.

In the present study, the activity of SOD significantly decreased after 6 weeks p.i. with *S. mansoni*. The decrease in SOD may result from production of H_2O_2 during oxidative metabolism as indicated by Pinteaux *et al*. (1996). The reduced antioxidant production was due to increased oxygen metabolites causing a decrease in the activity of antioxidant defense system. SOD is an important defense enzyme which catalyzes the dismutation of superoxide radicals (McCord *et al*., 1971). In our data and other reports, relatively low content of antioxidant enzymes in kidney and testes may cause it more vulnerable to oxidative stress. However, BER almost restored the renal and testesticular SOD activity to near control levels. Also, our results indicate that the preventive effects of BER may be due to scavenging of free radicals by its antioxidant nature.

Furthermore, the present data reveals a highly significant and progressive reduction in CAT activity post *S. mansoni* infection. In agreement with this, Gharib *et al*. (1999) showed that peroxide dismutation yields H_2O_2 which is detoxified by CAT resulting in decrease in its activity. In a recent study, Hanna *et al*. (2005) added that eosinophil peroxidase and its substrate H_2O_2 are released by inflammatory cells in the immediate vicinity of parasite eggs

Moreover the present results indicated that infection with *S. mansoni* impairs the antioxidant system reflected in the depleted level of GPx which is used as an index of oxidative stress and a sign that tissues are utilizing more antioxidant defenses(Ip *et al*., 2000).

Previous studies have described changes in reproductive hormones in various species following *S. mansoni* infection, but several reports are contradictory. According to Lansoud-Soukate *et al*. (1991) and Kasilima *et al*. (2004), *S. mansoni* caused a significant decrease in testosterone in infected mice, while Marzouki and Amin (1997) reported decreased serum levels of testosterone. In contrast, Abdallah *et al*. (1994) observed elevated levels of sex hormones in murine *S. mansoni* infection at 60 and 70 days post-infection, but also recorded a significant fall in testosterone and 17β-estradiol in female and male mice, respectively, 80 days post-infection. It is worth noting that several researchers have reported that testosterone and dehydroepiandrosterone acetate offer protection in mice challenged with cercariae and have proposed that serum levels of the two hormones are negatively correlated with schistosome worm burden (Kasilima *et al*., 2004; Morales-Montor *et al*., 2001).

CONCLUSIONS

In conclusion, the increased level of oxidative stress markers and the decreased level in antioxidant enzymes of kidney and testes are responded to schistosomiasis in mice. The findings of the present investigation suggest that BER exerts its beneficial effects on *S. mansoni*-induced oxidative stress may be attributed to its antioxidant activity, which could find clinical use in treating kidney and

testes dysfunction in schistosomiasis. But to elucidate the exact mechanism of this modulatory effect, and to examine its potential therapeutic effects further studies are necessary.

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