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ANTI-SCHISTOSOMAL AND ANTIFIBROTIC EFFECTS OF RESVERATROL LOADED ON NIOSOMES IN MURINE SCHISTOSOMIASIS MANSONI

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Abstract

Schistosomiasis is one of the most prevalent parasites causing morbidity. Praziquantel (PZQ) is recommended drug for all *Schistosoma* spp. But, it exhibits low and erratic bioavailability and drug resistance. This study evaluated the anti-parasitic and anti-fibrotic effects of resveratrol (RSV) loaded on niosomes in murine schistosomiasis *mansoni.* Mice were divided into 3 groups: GI (control) subdivided into (Ia) uninfected untreated, (Ib) infected untreated, and (Ic) infected treated with niosomes nanoparticles (NPs). GII: received niosomes-PZQ and subdivided into (IIa) received a dose of 250mg/kg body weight /24hrs in 2 doses of 3hrs apart at 4th wk. P.I. (antiparasitic) and (IIb) received a dose of 500mg/kg body weight divided equally on 2 consecutive days at 10th wk. P.I. (antifibrotic). GIII: subdivided into 2 subgroups (IIIa & IIIb) received niosomes-RSV in a dose of 20mg/kg bodyweight /24hrs 3 times a week for 2 wks. at 4th & 10th wks. P.I. respectively. All mice were subjected to parasitological, histopathological, & immunohistochemical (α-SMA) studies, as well as, ALT & AST serum levels evaluation. Niosomes-RSV caused significant reduction in adults' count, hepatic eggs, ALT & AST levels and hepatic granulomas' size and number. Niosomes NPs alone caused significant reduction only in adults' count and hepatic eggs compared to infected untreated ones.

Keywords: Schistosomiasis *mansoni*, Hepatic fibrosis, Resveratrol, Niosomes, α-SMA.

Introduction

Schistosomiasis is one of the most important parasitic diseases worldwide as the second risky parasite after malaria in morbidity and economic impact (Ali *et al*, 2016). Praziquantel (PZQ) proved to be the effective drug for all schistosomes, safe and low cost. But, PZQ displayed poor efficacy against *Schistosoma* eggs, schistosomula, and juvenile forms (de Oliveira *et al*, 2014), with poor water solubility for sufficient concentration in tissues and development of resistance (Doenhoff *et al*, 2008). Thus, there was a bad need for alternative chemotherapy(s) for schistosomiasis (da Silva *et al*, 2017). Egyptian medicinal plants proved to be alternative sources as against many parasites (Abo-Madyan *et al,* 2004; Abouel-Nour *et al,* 2016).

Resveratrol (RSV) is a naturally non-flavonoid polyphenol compound in many plants, such as grapes, berries, peanuts, and pines with so many medicinal values (Koushki *et al,* 2018). RSV have anti-inflammatory, antioxidant, anti-fungal, antiviral, antibacterial, and anti-parasitic effects alone or loaded with other compounds (Pace-Asciak *et al*, 1995; Docherty *et al*, 1999; Chan *et al*, 2002; Baur and Sinclair, 2006; Kedzierski *et al*, 2007; Lucas *et al*, 2013), and preventing liver fibrosis (Chávez *et al*, 2008; Zhang *et al*, 2016). However, RSV has low water solubility with rapid metabolism and clearance rates, which affect absorption and bioavailability limiting its value (Baur and Sinclair, 2006). Zu *et al*. (2016) reported that the increasing water solubility enhanced oral absorption and improving the bioavailability problems. They added that synthetic water-soluble drug, cyclodextrin inclusion and nanotechnology improved the efficacy of poorly soluble drugs

The potential of nanoparticles offer numerous advantages compared with other conventional treatments due to their greater design flexibility to improve the physicochemical, pharmaceutical &pharmacological properties of many less soluble drugs (Haggag *et al*, 2016; 2020). Niosomes are vesicles com-

posed of non-ionic surface-active agent bilayers, which serve as novel drug delivery systems (Bhardwaj *et al*, 2020), with many advantages as chemical stability, biodegradability, biocompatibility, low production cost, easy storage and handling, and low toxicity (Katare *et al*, 2006). Niosomes are used as a carrier to deliver different types of drugs such as synthetic and herbal, antigens, hormones, and other bioactive compounds (Bagheri *et al*, 2014; Sudheer *et al*, 2015; Singh Shikha *et al*, 2015).

This study aimed to investigate the antiparasitic and anti-fibrotic effects of resveratrol loaded on niosomes in comparison with praziquantel loaded to niosomes in murine schistosomiasis *mansoni*.

Materials and Methods

Experimental animals: The present study was carried out on 130 laboratory bred parasite free male Swiss albino mice, 4-5 weeks old with an average weight of 20-25 gm. Mice were obtained from Theodor Bilharz Research Institute. Mice were subcutaneously infected with 60 *S. mansoni* cercariae/ mouse (Holanda *et al*, 1974), and were kept controlled conditions (25°C, with 12hrs light & 12hrs dark cycle) in standard cages and maintained on a commercial pellet diet and water ad libitum.

Drug regimen: Praziquantel (PZQ) powder and resveratrol (RSV) powder were purchased from Sigma-Aldrich Chemie (Steinheim, Germany). Niosomes nanoparticles were used as a carrier to PZQ and RSV before given to experimental mice.

Niosomes were prepared using theses reagents and chemicals: Poly (ethylene glycol)-block-poly (propylene glycol)-block-poly (ethylene glycol) (Sigma-Aldrich Chemie, Steinheim, Germany), Span 60 and Cholesterol (El-Gomhouria Co.) and Ethanol.

Niosomes-PZQ was used in two concentrations as follow: 250 mg/kg bodyweight /24 hrs in two doses of 3 hrs, apart (Ismail *et al,* 1996) as an antiparasitic drug & 500mg/kg bodyweight divided equally on 2 consecutive days (Rewisha *et al*, 2003) as an antifibrotic drug. Niosomes-PZQ was prepared by hydrating niosome proconcentrate followed by bath sonication (Alomrani *et al*, 2011). Dispersion of the vesicles in the free drug solution could maintain the entrapped drug for a longer time due to equilibrium between the free and entrapped drug (El Maghraby, 2010).

Niosomes-RSV: It was used in a dose of 20 mg/kg bodyweight /24hrs three times a week for 2 consecutive weeks to assess both antiparasitic and anti-fibrotic effects. Preparation of niosomes-RSV began with hydration of a surfactant and lipid mixture at elevated temperatures, followed by optional niosome size reduction to obtain a colloidal suspension by the conventional thin-film hydration method (Yeo *et al*, 2017; 2018).

Study design: Mice were divided into 3 groups: GI (Control): included 50 mice subdivided into 3 subgroups (SGs): SGIa: 10 normal control), SGIb: 20 infected untreated, & SGIc: 20 infected treated with niosomes NPs. GII: 40 mice given niosomes-PZQ and subdivided into 2 subgroups. SGIIa: 20mice given niosomes-PZQ in a dose of 250mg/kg bodyweight /24hrs in 2 doses of 3hrs apart at 4^{th} week P.I. SGIIb: 20 mice given niosomes-PZQ in a dose of 500mg/kg bodyweight divided equally on 2 consecutive days at 10^{th} week P.I. (early hepatic fibrosis stage). GIII: 40 mice given niosomes-RSV in a dose of 20mg/kg body weight /24hrs 3 times a week for 2 consecutive weeks and were subdivided into (IIIa, IIIb) as previously mentioned.

Two weeks after last dose of treatment, all mice were sacrificed to collect sera that were kept frozen at -20˚C until needed to measure liver enzymes. Sacrificed mice were subjected to parasitological, histopathological, immunohistochemical (α-SMA) studies,& biochemical analysis ALT &AST serum levels.

Parasitological studies: Hepatic and portomesenteric vessels perfusion were done to recover and subsequent count of adult schistosomes (Duvall and Dewitt, 1967). Liver egg counts were detected in all infected mice as follows; 1gm from each liver was put in

2ml of 5% KOH in a test tube and kept overnight at room temperature. All tubes were incubated for 6hrs at 37°C. For *S. mansoni* eggs count, each tube was shaken, 0.1ml of digest was examined microscopically for total egg counts (Cheever, 1968).

Histopathological study: Liver sections were fixed in 10% neutral buffered formalin, processed for paraffin blocks. Liver sections were stained with hematoxylin and eosin (H&E). For each section, granulomas were counted in ten high power fields and the largest diameter of the liver granulomas was measured using the Image J software available at the website (http://rsb.info. nih.gov/ij/) and the mean diameter of granulomas / liver sections was then calculated.

Immunohistochemical study: Liver sections were deparaffinized in xylene, rehydrated in descending ethanol and washed in phosphate buffer saline (PBS). Antigen retrieval was done by exposing sections in citrate buffer (pH 6.0) to 10min of microwaves and then immersed in 3% hydrogen peroxide for blocking endogenous peroxidase. Background staining was blocked by puting slides in Ultra V Block. An overnight incubation of sections with monoclonal mouse anti α-SMA (Labvision catalog No. MS-146-R7) antibody was done at room temperature in a humid chamber. Sections were washed with PBS and after incubating slides with biotinylated goat anti-polyvalent, streptavidin peroxidase for 10min. each, diaminobenzidine tetrachloride (DAB) was used as a chromogen; slides were stained in Meyer's hematoxylin and mounted in (DPX).

Biochemical study: Blood was centrifuged at 3000rpm for 15min. to separate sera that were stored at -20˚C until needed (Biosystems, Spain). The AST& ALT levels were measured in all mice as compared to control.

Ethical approval: The study was approved according to Guidelines of Laboratory Animal Centre for Research Ethics Committee of Faculty of Medicine, Tanta University (Approval code 34203/10/20).

Statistical analysis: Data were analyzed by using SPSS (Statistical Package for Social Studies, version 22). Qualitative data were presented as number and percent, and were described as mean, standard deviation (SD) and reduction percentage. Parametric tests were applied for normally distributed data such ANOVA (Analysis of Variance). For categorical variables, Chi-square test was used for analysis. Post Hoc test was used to detect significance. Differences were not significant if $P > 0.001$ and highly significant if $P < 0.001$.

Results

Adult *Schistosoma mansoni* worm count: There was a significant decrease in both niosomes-PZQ & niosomes-RSV groups without significant difference between groups at 4 & 10 weeks P.I. as compared to niosomes control. Egg count at 4 &10 weeks P.I. mean number of eggs/gm liver was significantly decreased in niosomes control, niosomes-PZQ, and niosomes-RSV groups.

Histopathological study: Hepatic granulomas/liver section at 4 & 10 weeks P.I., showed a significant decrease in niosomes-PZQ and niosomes-RSV groups as compared to infected and niosomes control ones, without significant difference between both.

Diameter of granulomas showed a significant decrease in mean diameter of hepatic granulomas in niosomes-PZQ & niosomes-RSV groups as compared to infected control at 4 & 10 weeks, reduction percent in niosomes-RSV group was more significant as compared to niosomes-PZQ group.

Histopathological examination of liver sections at 4 weeks P.I. of infected untreated and niosomes treated mice showed multiple portal and parenchymal granulomas mainly of cellular types. Cellular granulomas showed a collection of inflammatory cells of eosinophils, histiocytes, epithelioid cells with sc anty fibrous tissue. Granulomas Niosomes-PZQ decreased significantly and some granulomas were fibro-cellular formed of few epithelioid cells with mild fibrous tissue. Niosomes-RSV ones showed a marked reduction in granulomas' size mainly to fibro-cell-

ular type.

At 10 weeks P.I., liver of infected untreated and niosomes treated mice showed multiple granulomas, majority were of fibrocellular type. Niosomes-PZQ effect on treated mice, number and size granuloma were significantly reduced as compared to infected control. Granulomas were mainly of fibrous type consisted of fibroblasts and few histocytes. In niosomes-RSV, liver sections showed fibrous granulomas composed mainly of fibroblasts and few histiocytes with great reduction in number and size.

Immunohistochemical study showed that immunoreactivity of α-SMA in hepatic tissues of all groups at different durations P.I, a significant increase in α-SMA expression by HSCs at 4 & 10 weeks as compared to control. A marked significant increase in α-SMA expression was in niosomes-PZQ mice graded as moderate and niosomes-RSV ones graded as high as compared to infected or niosomes controls graded as low and moderate respectively.

Biochemical study showed significant reduction in mean AST & ALT levels in niosomes-PZQ and niosomes-RSV mice compared to infected control at 4 & 10 weeks.

Details were given in tables (1, 2, 3 & 4) and figures (1 & 2).

Table 1: Comparison of total adult worm loads and hepatic egg counts recovered from different infected groups.

Items		Mean± S. D	F. test	p. value	Post Hoc test			
Adults' count at 4 weeks P.I.	Infected control	13.00±4.14	10.513	0.001*	P1	0.347	P4	0.002*
	Niosomes control	11.50±1.84			P2	0.001*	P5	0.001*
	Niosomes–PZQ	7.05±3.91			P3	0.001*	P6	0.789
	Niosomes–RSV	6.75±3.43						
Adults' count at 10 weeks P.I.	Infected control	8.60±1.17	9.955	0.001*	P1	0.007*	P4	0.271
	Niosomes control	6.00±1.63			P2	0.001*	P5	0.040*
	Niosomes–PZQ	5.10±2.45			P3	0.001*	P6	0.231
	Niosomes–RSV	4.30±2.23						
Liver egg count at 4 weeks P.I.	Infected control	15414.20±1093.14	72.452	0.001*	P1	0.001*	P4	0.001*
	Niosomes control	10752.50±1414.30			P2	0.001*	P5	0.001*
	Niosomes–PZQ	5487.00±2387.47			P3	0.001*	P6	0.461
	Niosomes–RSV	5947.05±2024.69						
Liver egg count at 10 weeks P.I.	Infected control	18493.90±2596.06	15.332	0.001*	P1	0.013*	P4	0.001*
	Niosomes control	16001.50±2886.23			P2	0.001*	P5	0.001*
	Niosomes–PZQ	10896.60±3356.83			P3	0.001*	P6	0.855
	Niosomes–RSV	11122.65±5144.43						

Table 2: Number & mean diameter of granulomas in all infected groups.

Items		Mean± S. D	F. test	p. value	Post Hoc test			
Granulomas /section at 4 weeks P.I.	Infected control	26.30±6.18	43.056	0.001*	P1	0.675	P4	0.001*
	Niosomes control	25.40±5.95			P2	0.001*	P5	0.001*
	Niosomes–PZQ	9.60±3.20			P3	0.001*	P6	0.457
	Niosomes–RSV	8.00±2.58						
Granulomas /section at 10 weeks P.I.	Infected control	24.80±5.81	55.181	0.001*	P1	0.434	P4	0.001*
	Niosomes control	23.20±5.75			P2	0.001*	P5	0.001*
	Niosomes–PZQ	7.80±3.29			P3	0.001*	P6	0.062
	Niosomes–RSV	3.90±2.02						
Granuloma size (μ) at 4 weeks P.I.	Infected control	2.49±0.27	38.704	0.001*	P1	0.263	P4	0.001*
	Niosomes control	2.40±0.32			P2	0.001*	P5	0.001*
	Niosomes–PZQ	1.04±0.06			P3	0.001*	P6	0.002*
	Niosomes–RSV	0.86±0.07						
Granuloma size (μ) at 10 weeks P.I.	Infected control	1.77±0.10	78.499	0.001*	P1	0.240	P4	0.001*
	Niosomes control	1.72±0.10			P2	0.001*	P5	0.001*
	Niosomes–PZQ	0.67±0.08			P3	0.001*	P6	0.001*
	Niosomes–RSV	0.450.09						

Table 3: Comparison of α-SMA expression in groups at different durations P.I.

Groups	4 weeks P.I.			10 weeks P.I.		
	Low	Moderate	High	Low	Moderate	High
Infected control	10(100%)	0 (0%)	0 (0%)	0 (0%)	10(100%)	0 (0%)
Niosomes control	10(100%)	0 (0%)	0 (0%)	0 (0%)	10(100%)	0 (0%)
Niosomes–PZQ	2 (20%)	7 (70%)	1 (10%)	1 (10%)	1 (10%)	8 (80%)
Niosomes–RSV	1 (10%)	8 (80%)	1 (10%)	0 (0%)	1 (10%)	9 (90%)
Chi square	29.786			34.845		
p. value	0.001*			0.001*		

Table 4: Mean values of AST and ALT levels in all studied groups.

Items		Mean± S. D	F. test	p. value	Post Hoc test			
AST at 4 weeks P.I.	Healthy control	216.20±44.32	26.096	0.001*	P1	0.826	P4	0.001*
	Infected control	523.20±64.55			P2	0.001*	P5	0.001*
	Niosomes control	515.76±73.74			P3	0.001*	P6	0.878
	Niosomes–PZQ	336.36±71.70						
	Niosomes–RSV	340.05±88.38						
ALT at 4 weeks P.I.	Healthy control	38.60±5.41	17.379	0.001*	P1	0.797	P4	0.001*
	Infected control	164.05±38.48			P2	0.001*	P5	0.001*
	Niosomes control	167.76±29.95			P3	0.001*	P6	0.954
	Niosomes–PZQ	118.85±45.10						
	Niosomes–RSV	119.44±9.96						
AST at 10 weeks P.I.	healthy control	217.80±36.64	4.893	0.001*	P1	0.865	P4	0.001*
	Infected control	506.70±76.39			P2	0.001*	P5	0.001*
	Niosomes control	514.20±64.03			P3	0.001*	P6	0.684
	Niosomes–PZQ	362.94±108.62						
	Niosomes–RSV	350.23±117.32						
ALT at 10 weeks P.I.	healthy control	40.20±3.96	6.058	0.001*	P1	0.547	P4	0.001*
	Infected control	173.30±29.23			P2	0.001*	P5	0.001*
	Niosomes control	182.60±21.81			P3	0.001*	P6	0.394
	Niosomes–PZQ	110.15±47.89						
	Niosomes–RSV	100.83±28.17						

Discussion

Schistosomiasis is more or less an endemic disease distributed worldwide particularly in the developing countries including Egypt (WHO, 2016). PZQ is considered the mainstay for control and elimination of schistosomiasis in humans. This is based on its low cost and easy administration as well its high patient tolerability (Le Clec'h *et al*, 2021). Unfortunately, the drug has poor water solubility and has not been effective in treating the early forms of schistosome species (Gryseels *et al*, 2006), with a bad need for a new drug including niosomes nanoparticles (NPs) as a vehicle for delivery of poorly absorbable drugs (Adekiya *et al*, 2020). The RSV proved to be one of the natural polyphenols with a very high antioxidant potential (Fracasso *et al*, 2021).

In the current study, at 4th and 10th weeks P.I. there was a significant reduction in mean adult counts, hepatic egg loads, number and diameter of hepatic granulomas in mice treated with niosomes-PZQ and niosomes-RSV without significant difference. This showed that both have equivalent potent effect on *S. mansoni* adult with improving PZQ bioavailability after niosomal encapsulation (El-Feky *et al*, 2015). The administration of niosomes alone gave some activity against adults with reduction rate of 30.23% at 10th weeks P.I. This agreed with Zoghroban *et al.* (2019) who reported moderate contracture and destruction in the parasite morphology on using niosomes alone. Also, the niosomes- PZQ agreed with others (Radwan *et al*, 2019; Silva *et al*, 2021).

Chen *et al*. (2019) reported that RSV reduced the worm count and damaged its tissues. In an in-vitro study of RSV, adults were convoluted, contracted and stiff exhibiting drastic local swelling (Schneider *et al*, 2003), as well as tubulin polymerization of adult schistosome (Chabert *et al*, 2006). Soliman *et al.* (2018) found that mice treated with RSV only mildly red-uced the mean

total number of worm burden that indicated RSV effect on the neuromotor activity which in turn could degrade the ability of adults to migrate for nutrients (Soliman *et al*, 2017). Machado *et al.* (2021) found that the niosomal drug delivery system stabilized RSV, preventing degradation, improving dispersibility in water with antioxidant activity.

In the current study, reduction of *S. mansoni* eggs per gram liver in niosomes-RSV treated mice referred to RSV effect on the adults themself. This agreed with Soliman *et al*. (2018) who reported that RSV treated mice decreased the mean hepatic and intestinal egg load with significantly increased dead ova compared to control group.

In the current study, granulomas diameter in niosomes-RSV treated mice showed a higher reduction percentage compared to niosomes-PZQ treated ones. This agreed with Soliman *et al.* (2018) who found that RSV caused had a high reduction 91.1% as compared to PZQ. This agreed with Gouveia *et al*. (2019) who reported that RSV affected the schistosomes, and its anti-oxidase improved liver fibrosis. Sultan *et al*. (2018) reported that niosomal encapsulation prolonged drug delivery, absorbed by oral administration, and enhanced its bioavailability.

In the present study, both niosomes-PZQ & niosomes-RSV at 4^{th} or 10^{th} weeks P.I. showed a marked decrease in number and size of granulomas and more decrease in inflammatory cells as compared to others. Also, Zoghroban *et al*. (2019) reported a weak antifibrotic action on liver when compared with PZQ alone to niosomes-PZQ. The superiority of niosomes-RSV therapy was attributed to have antioxidative, anti-inflammatory, antifibrogenic and antiproliferative, with significant diminution of cell mediated response to soluble egg antigens (Soliman *et al*, 2018).

Hepatic fibrosis is a major feature of liver injury in chronic schistosomiasis (Friedman, 2003), with damage of liver and HSCs activation to excess production of extracellular matrix (ECM) components (Bartley *et al*, 2006) and severe oxidative stress to the fibrosis central event (Nieto *et al*, 2002). Although α-smooth muscle actin (α-SMA) is normal positive in a few HSCs, yet expressed significantly increased in chronic infection by activation of stellate cell showing a myofibroblastic phenotype (Hautekeete and Geerts, 1997). The present results suggested that the collagen content in granulomatous liver gradually increased with infection progression. This agreed with both Martinelli *et al*. (2004) and Carotti *et al*. (2008) who found an association between α-SMA-positive HSCs and degree of fibrosis.

In the present study, niosomes NPs alone didn't show significant difference in α-SMA expression from infected untreated without affecting liver fibrosis. There was a highest increase in α-SMA expression in niosomes-PZQ & niosomes-RSV at 10^{th} weeks P.I., as PZQ and RSV exhibited antifibrotic activity. This agreed with Wu *et al*. (2019).

In the current study, weak antifibrotic activity of these drugs was due to optimum antifibrotic effect in a dose-dependent manner and the drug duration. This agreed with Ismeil *et al*. (2016) reported that when RSV I.P. in a dose of 20mg/kg body weight, twice/week started 4^{th} weeks P.I. up to the 10^{th} week, exerted great antifibrotic effect by down-regulating fibronectin gene expression, and preventing liver fibrosis development and increased TNF-α serum levels in positive control. Soliman *et al*. (2018) reported that *S. mansoni*-infected mice treated with RSV (20mg /kg/day) once daily for 2 weeks at 6^{th} weeks P.I. improved fibroblastic proliferation and fibrosis compared to positive mice scarified at end of 10^{th} week P.I. Chen *et al*. (2019) reported that RSV orally in a dose of 400mg/kg body weight at 6^{th} weeks P.I. for 3 days, mice were euthanized at 8^{th} & 10^{th} weeks P.I, with fibrosis reduction.

In the present study, AST & ALT levels in niosomes control mice didn't show significant difference compared to positive control at all durations P.I. This agreed with Amer

et al. (2022) who reported that niosomes structure materials as cholesterol incorporation; Span 60 and non-ionic surfactant were safe, neither toxic nor irritant.

In the present results, niosomes-PZQ and niosomes-RSV groups showed a significant reduction of AST & ALT levels, but without significant difference as compared to positive control. This reduction was either restoration of oxidant/antioxidant balance or a reduction in hepatic granuloma size and amelioration of necrotic liver tissue in positive control (Hamed and Hetta, 2005). This agreed with Adikwu *et al*. (2019) who reported that the antioxidant activity of RSV restored the hepatic markers levels by facilitating regenerative ability of hepatocytes. The intra-peritoneal administration of RSV to schistosomal infected mice remarkably attenuated the levels of liver enzymes almost towards the basal levels (Ismeil *et al*, 2016)

Conclusion

The niosomes-RSV caused reduction in worm count, tissue eggs load and attenuated *S. mansoni*-induced AST & ALT elevation. It decreased liver granulomas' number and showed better results than niosomes-PZQ as to granulomas' size. However, RSV didn't have sufficiently action on fibrosis degree, with result of SSLF severity even after RSV treatment.

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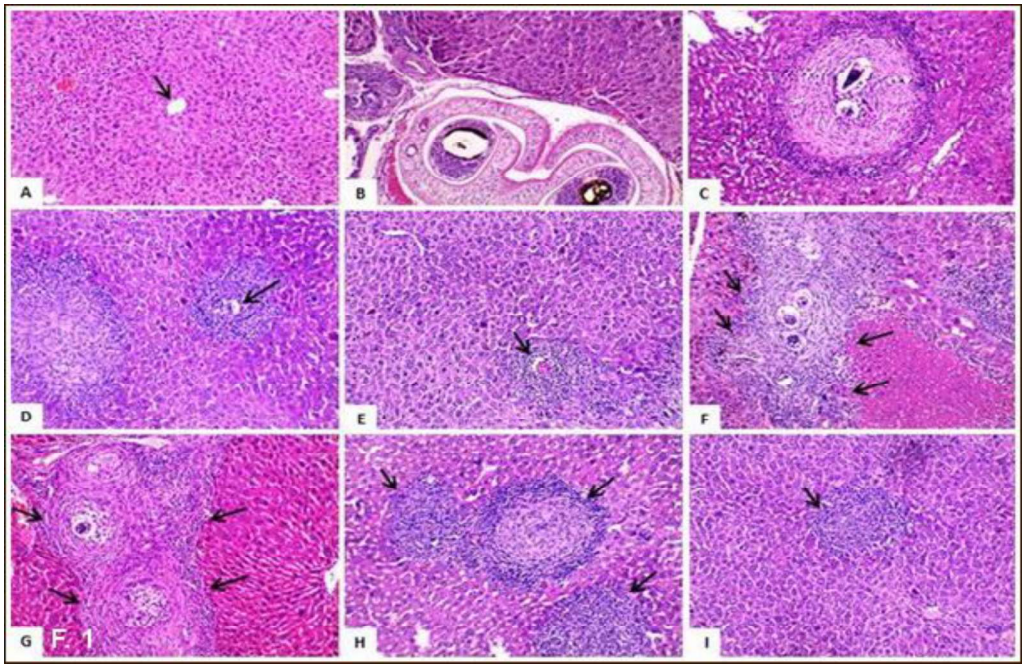
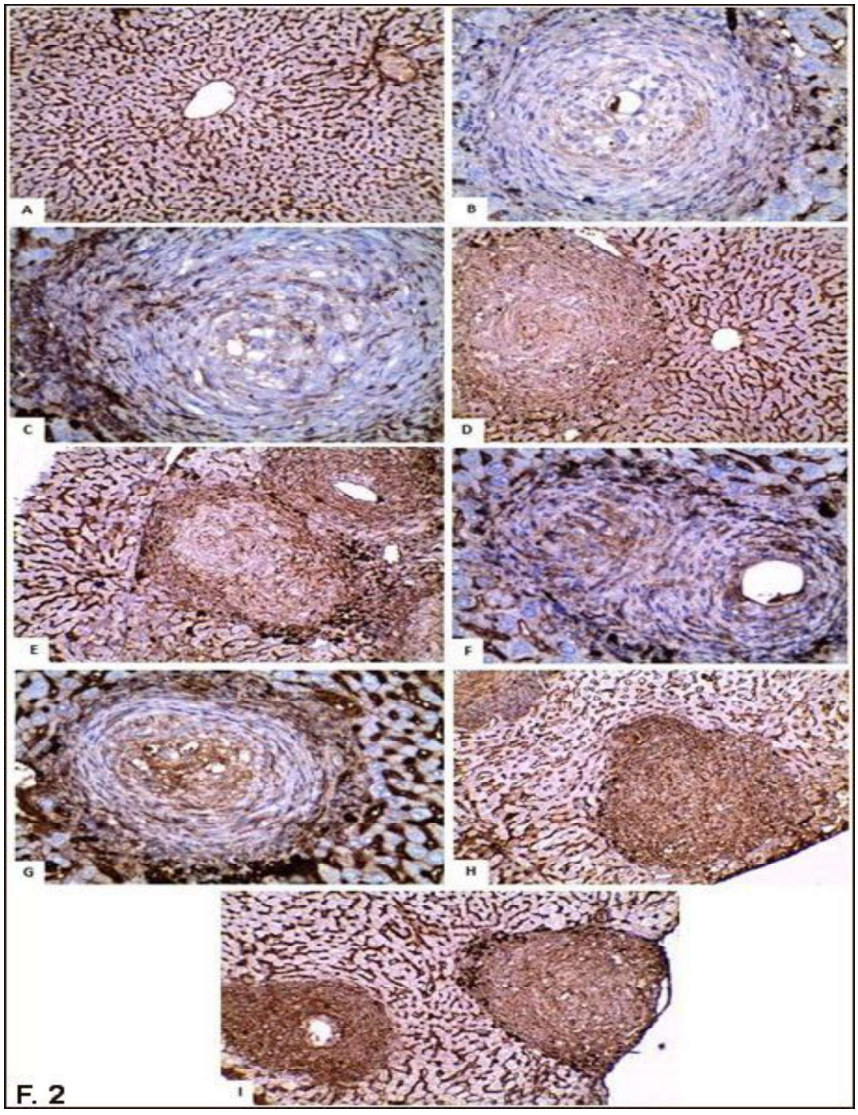
Explanation of figures

Fig. 1: Liver section (H & E, x200) A- Healthy control showed polygonal hepatocytes with small rounded nuclei arranged in plates with sinusoids in-between arranged around central vein (arrow). B- Infected untreated control 4 weeks P.I. showed adults in hepatic portal tract. C- Niosomes control 4 weeks P.I. showed large granuloma around viable ova surrounded by eosinophils, histiocytes, epithelioid cells with scanty fibrous tissue. D- Niosomes-PZQ treated 4 weeks P.I. showed decrease in granulomas size around viable ova (arrow), Granulomas of fibro-cellular type, of histiocytes, few epithelioid cells with fibrous tissue. E- Niosomes-RSV treated 4 weeks P.I. showed marked reduction in granulomas size as compared to infected untreated control with mild fibrous tissue (arrow). F- Infected untreated control 10 weeks P.I. showed multiple schistosomal granulomas coalescent with each other mainly of fibro-cellular type (arrow) around viable ova. G- Niosomes control 10 weeks P.I. showed multiple granulomas coalescent mainly of fibro-cellular type (arrow) around viable ova. H- Niosomes–PZQ treated 10 weeks P.I. showed multiple schistosomal granulomas with decreased size (arrow), granulomas mainly of fibrous type of fibroblasts and few histiocytes. I- Niosomes-RSV treated 10 weeks P.I. showed marked reduction in granulomas size (arrow), Granulomas mainly fibrous type of fibroblasts and few histocytes.

Fig. 2: Liver section ((Immunoperoxidase) A- Uninfected control showed +ve α-SMA immunoreactivity expression by HSCs (×200). B- Infected untreated control 4 weeks P.I. showed low immunoreactivity for α-SMA in HSCs (×400). C- Niosomes control 4 weeks P.I. showed low immunoreactivity for α-SMA in HSCs (×400). D- Niosomes-PZQ treated 4 weeks P.I. showed moderate immuno-reactivity for α-SMA in HSCs (×200). E- Niosomes-RSV treated 4 weeks P.I. showed moderate immunoreactivity for α-SMA in HSCs (×200). F- Infected untreated control 10 weeks P.I. showed moderate immunoreactivity for α-SMA in HSCs (×400). G- Niosomes control 10 weeks P.I. showed moderate immunoreactivity for α-SMA in HSCs (×400). H- Niosomes–PZQ treated 10 weeks P.I. showed high immunoreactivity for α-SMA in HSCs (×200). I- Niosomes–RSV treated 10 weeks P.I. showed high immunoreactivity for α-SMA in HSCs (×200).





F. 2