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RESEARCH

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Schistosomicidal and immunomodulatory effects of *Momordica charantia* in *Schistosoma mansoni*-infected mice

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Abstract

Background The current work was designed to evaluate the influence of *Momordica charantia* fruit (MCF) supplement alone (200 mg MCF/kg) or with praziquantel (250 mg PZQ/kg) in *Schistosoma mansoni*-infected mice. Parasitological parameters, scanning electron microscopy (SEM) of male adult worm of *S. mansoni*, histopathological and immunohistochemical alterations of liver and intestine, antioxidant activity, cytokine changes, and flow cytometric analysis of the blood $CD4^+$ and $CD8^+$ cells were detected.

Results The phytochemical screening of bitter melon fruit revealed good contents of phenols and flavonoids. Dual treatment of PZQ plus MCF showed elimination of worm burden as the reduction percentage was (100%) compared to treatment with PZQ alone (44.4%). All treatments revealed a tegumental damage of the parasite associated with a significant decrease in liver and intestine ova count, a significant elevation in the percentages of dead ova, and a partial decrease in granuloma diameter. Dual treatment (PZQ + MCF) had the highest significant decrease in mean number of hepatic and intestinal granuloma diameter; the decrease was (60.59 ± 8.0 and 35.77 ± 7.10), respectively in comparison with the infected group (158.57 ± 34.32 and 69.46 ± 13.56). All these alterations were accompanied by a lowering in the level of IFN-γ (365.40 ± 4.55), and a rise in IL-10 level (76.25 ± 2.78), $CD4^+$ and $CD8^+$ cells (51.18 ± 3.31, 49.68 ± 0.54) respectively in MCF-treated group compared to infected mice (400.90 ± 14.67, 66.90 ± 4.31, 41.58 ± 1.37, 34.78 ± 3.79). The antioxidant status showed a significant increase in infected mice treated alone with MCF or combined with PZQ compared to the infected group.

Conclusions These outcomes can deduce that dual treatment (PZQ + MCF) has a curative impact on *S. mansoni* infection and contribute to reducing hepatic and intestinal histopathological effects via modulating host immune response and antioxidant status.

Keywords Schistosomiasis, *Momordica charantia*, Granuloma, Immunomodulation, Scanning electron microscopy

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Introduction

Schistosomiasis is one of the major health problems caused by parasitic helminths of genus *Schistosoma* that threaten human life in many countries [58]. *S. mansoni* is the Egyptian strain, one of the main neglected tropical waterborne diseases as a result of several environmental factors and behaviors that encourage snail survival in freshwater Africa [2]. The World Health Organization (WHO) estimated that intestinal Schistosomiasis (*S. mansoni*) affects globally at least 251.4 million people in Africa, the Middle East, the Caribbean, Brazil, Venezuela, and Suriname, and about 90% of them live in Africa [81]. Most pathology in *Schistosoma*-infected animals is attributed to the host's reaction to the eggs via destroying the host tissue cells and stimulating the development of severe inflammatory reactions around the egg by the fibrotic and antigenic material (granuloma) [54]. Comprehensive measures were performed by the Egyptian government, like snail control, hygiene education, mass chemotherapy, behavior changes, and environmental changes, which were effective in reducing the disease prevalence and morbidity, but unfortunately were unable to prevent re-infection [34]. To date, the treatment of Schistosomiasis remains based on Praziquantel (PZQ) which is known to be an effective drug against all types of Schistosomiasis [33], but it often does not completely end the parasitic infection due to its inactivity against young worms [11]. The lower solubility of PZQ in water causes its lower absorption through the intestine, and also its metabolism results in the production of a less potent compound [20]. PZQ is safe and effective against schistosomiasis, but there are some limitations to its use, such as issues of reinfection, some observed low cure rates, possible resistance, and frequent treatment failures [31]. So, PZQ was insufficient therapy in endemic areas [60]. These factors and drug resistance by *Schistosoma* parasites prompted scientists to search for natural products, especially medicinal plants to be used as an essential or a supportive agent against parasitic infection [20, 22, 38, 42, 63, 72]. These studies demonstrated that many plants due to their constituents had beneficial therapeutic properties, including anti-inflammatory, anticancer, antioxidant, antimicrobial, and immunomodulatory effects on experimental animals. The present work focused on agents selected from medicinal plants, due to their richness in flavonoid and polyphenolic compounds. *Momordica charantia* (Bitter melon, MC) is a perennial plant that develops naturally in tropical areas, which belongs to the family *Cucurbitaceae*. Its fruit *Momordica charantia* fruit (MCF) is a vegetable product that looks like a cucumber with a bitter taste. It is one of the most common traditional medicine herbs used for malaria treatment throughout the world [15]. The traditional uses of MC have been recorded in many countries due to the biological active ingredients in its fruit, leaf, and seed, including antiparasitic [67, 68], immunomodulatory [3, 42], anti-inflammatory [84], antioxidant [5], antidiabetic [41, 47], antiviral [18], anticancer [25], and antibacterial properties [78]. Interestingly, crude extracts from *M. charantia* have anti-helminthic activity against *Meloidogyne* spp. [64], *Fasciola hepatica* [16], and *Ascaridia galli* [44]. Studies on the chemical composition of extracts prepared from *M. charantia* fruits revealed the presence of triterpenoid glycosides [50]. However, chemical and biological analyses of extracts obtained from other parts of *M. charantia* plants are still necessary to identify the potential compounds responsible for the anti-helminthic properties reportedly associated with this plant [16]. To our knowledge, there is no research that has used bitter melon fruit against the intestinal Schistosomiasis, so biological investigations of the bitter melon fruit efficiency are needful to detect its anti-helminthic activity against different intestinal abnormalities. This study aimed to evaluate the potential effectiveness of MCF in combination with PZQ against intestinal Schistosomiasis on an experimental murine model.

Materials and methods

Drug and MCF supplement

Praziquantel tablets (PZQ, Epiquantel) was purchased from the Egyptian International Pharmaceutical Industries Company (EIPICO). PZQ was administered orally to the infected mice as an aqueous suspension, freshly prepared at a total dosage of 250 mg/kg body weight for three alternate days (1, 3, and 5) after infection [63, 76]. *Momordica charantia* fruit supplement (500 mg per capsule) was manufactured by Nutraceutical Corporation, Solaray (USA). MCF was dissolved in distilled water and given orally to each mouse in a dose of 200 mg/kg body weight daily for 4 days after infection [15].

Phytochemical and antioxidant contents of MCF

The phytochemical contents, such as phenolic and flavonoid components, were quantitatively analyzed to estimate the chemical profile of bitter melon fruit supplement. The total phenol content in MCF was determined by the Folin-Ciocalteu method using gallic acid as the standard agent [74]. The flavonoid in MCF was recorded according to aluminum chloride colorimetric method [12, 13]. The antioxidant activity of MCF was assessed by applying DPPH free radical assay. The 2-diphenyl-2-picryl hydrazyl hydrate (DPPH) radical scavenging activity was recorded in terms of % Inhibition [65].

Animals

Healthy adult male CD1 strain albino mice 6–8 weeks old, weighing between 22 and 25 g and laboratory-breed *Biomphalaria alexandrina* snails infected with miracidiae of the Egyptian strain of *S. mansoni* were utilized. They were acquired from *Schistosome* Biological Supply Unit, Theodor Bilharz Research Institute, Egypt. Mice were transported to the animal house, 1 week before initiation of the experiment, for acclimatization to laboratory conditions and housed in plastic cages. Experimental procedures were carried out after permission from the Institutional Animal Ethical Committee, Menoufia University, Egypt (Approval ID: MUFS/S/Pa/1/22).

Schistosomiasis infection

After 4 weeks of *Biomphalaria alexandrina* snail infection, they were kept in dechlorinated tap water and then exposed to artificial light at 28 °C for 2 h to stimulate cercariae shedding [75]. Each mouse was subcutaneously injected with freshly shed cercariae (60 ± 10) [38].

Experimental design

Forty male albino mice were used in the current research and grouped into 5 groups (8 mice per group). Healthy control mice without infection or any treatment (G1, uninfected healthycontrol). Infected mice "with freshly shed cercariae" without treatment (G2 infected positive control). After 6 weeks post-infection, the infected mice were treated with aqueous suspension of PZQ (250 mg PZQ/kg) orally on three alternate days (1, 3, and 5) (G3, PZQ, mono treatment) [63, 76]. The infected mice were treated with *Momordica charantia* fruit supplement (200 mg MCF/kg) administered orally daily for four consecutive days (G4, MCF, mono treatment) [15]. Mice were treated with both PZQ and MCF at the previous doses in G3 and G4 (G5, PZQ + MCF, dual treatment).

Sample collection

At the end of the experiment, blood samples were collected in centrifuge tubes for biochemical assays (Serum samples were stored at − 20 °C until used) and other blood sample was collected in heparinized tube for the separation of leukocytes for flow cytometry analysis. Mice of all groups were dissected immediately after decapitation at the end. Liver and intestine were separated from all mice groups and divided into 2 parts; the first part for parasitological parameters and the second one was fixed in 10% buffered neutral formalin for paraffin block preparation for histopathological and immunohistochemical studies.

Parasitological parameters

Perfusion of the mesenteric and portal veins was performed to retrieve worms in all mice to estimate worm burden [45]. The *S. mansoni* worms were classified according to sex and counted under a stereomicroscope (LW Scientific, GA, USA). The worm burden reduction percentage (%) in all groups was calculated [59, 62].

Wormburdenreduction% =
(Mean worm recovered from untreated control − mean worms recovered from the treatment group)/mean worms recovered from the untreated control group *100 [62].

Liver and intestinal small pieces weighed separately 0.5 g were dried on filter papers, placed in a glass test tube containing 5 ml of 4% potassium hydroxide (KOH) solution for tissue digestion. Ova counts per gram of liver or intestine were determined as defined by Cheever et al. [14]. The Oogram pattern of the various developmental stages of the eggs in liver and intestine was investigated [55].

Scanning electron microscopic technique of adult male worms

Adult male *S. mansoni* worms were collected from all mice groups and examined by scanning electron microscopy (SEM). The worms were primary fixed in 2.5% glutaraldehyde for 24 h at 4 °C, washed with phosphate buffer (pH 7.4) overnight at 4 °C, then secondary fixed with 1% osmium tetroxide for an hour. After that, dehydrated by serial dilution of ethanol (30–100%), dried, mounted on metal stubs, and coated with sputter coat of gold [56]. The worms were examined by Joel JSM-5300, Japan SEM at Faculty of Science, Alexandria University, Egypt. Magnified areas in the worms were photographed specially; the tubercles on the tegument and suckers.

Histological examination, granuloma measurement, and fibrosis score

Specimens of the liver and intestine were dissected from all mice groups and fixed in 10% neutral-buffered formalin (24 h) for paraffin block preparation [6]. Paraffin Sects. (5 µm) were stained with hematoxylin and Eosin (H&E) for histopathological examination and granuloma measurements, and Masson's trichrome staining for collagenous fibers deposition [7]. A quantified Ishak scoring system was utilized evaluate the hepatic fibrosis intensity on Masson trichrome-stained liver sections from current groups by the modified Knodell scoring system according to Ishak et al. [39] and Goodman [29], from 0 to 5 as follows: 0 indicates No fibrosis, 1 refers to fibrous in some portal areas with

or without short septa, 2 demonstrates fibrous in most of the portal areas with or without short septa, 3 indicates fibrous in most portal areas with portal to portal (PP) bridges, 4 refers to fibrous in portal areas with PP and portal-center (PC) bridges, 5 evaluates Pronounced PP and/or bridges, and 6 indicates Cirrhosis. Intestinal fibrosis was scored by a blinded observer on adjacent sections stained with Masson's Trichrome (stains collagen and proteoglycans) according to Hagenlocher et al. [32]. The scoring criteria used for fibrosis are 0 to 3 as follows: 0 refers to No increase collagen, 1 indicates a weak fibrosis: increased only low amounts and density of collagen in the submucosa, 2 demonstrates a moderate fibrosis: increased amount and density of collagen in submucosa and mucosa, and 3 refers to a severe fibrosis: increased collagen deposits in whole intestinal wall. The quantitative evaluation of collagen fibers was measured 10 figures/group, 10 ×magnification lens. The histopathological alterations were recorded, and granuloma diameter was measured by using an ocular micrometer at a low power field of a multi-head microscope according to Jacobs et al. [40]. Histological sections were photographed by Olympus BX 41 microscope (Japan), equipped with a digital camera.

Determination of total IgG, IL-10, and IFN-γ levels

The levels of total immunoglobulin G (IgG), anti-inflammatory cytokine interleukin 10 (IL-10), and the pro-inflammatory cytokine interferon-gamma (IFN-γ) in serum samples were estimated by enzyme-linked immunosorbent assays (ELISA) according to the manufacturer's instructions. Total IgG was determined using mice IgG ELISA Kit (Cat.No.E99-131, Bethyl Laboratories, Inc, USA). The concentration of mice IL-10 was determined by a sandwich ELISA Kit (Cat.No. EM2IL-10—Thermo-Scientific, USA). The quantitative detection of mice IFN-γ was determined using mice IFN-γ ELISA Kit (Cat.No.RAF022R-BioVendor, USA).

Evaluation of serum oxidative and antioxidant status

The level of the product of lipid peroxidation (malondialdehyde; MDA) was determined using the thiobarbituric acid assay according to the method described by Wills [83]. Nitric oxide (NO) level was assayed according to the method described by Montgomery and Dymock [61]. The activity of superoxide dismutase (SOD) was estimated by commercial kit (ZellBio GmbH, Germany) according to the method described by Heikkila and Cabbat [36]. Catalase (CAT) activity was estimated by a commercial kit (ZellBio GmbH, Germany) according to the method described by Goth [30].

Sub-typing of the immune cells

Sub-typing of the indicated immune cells was performed in whole blood as suggested by Hassouna et al. [35]. Briefly, mononuclear blood cells were prepared in RPMI-1640 (one million cells/ml). Anti-$CD4^+$ and Anti-$CD8^+$ cell subtypes were determined using fluorescence-activated cell sorting (FACS) flow cytometer (Becton Dickinson, Sunnyvale, CA) with Cell Quest Software for data acquisition and analysis using mice anti-CD4 or anti-CD8 monoclonal antibodies conjugated with fluorescein isothiocyanate (FITC; BD Biosciences, San Jose, CA).

Immunohistochemistry examinations ($CD3^+$ and $CD20.^+$ expression)

Liver and intestine paraffin Sections (4 µm) of all mice groups on charged slices were reacted specifically with $CD3^+$ and $CD20^+$ rabbit monoclonal antibodies according to the manufacturer's instructions (Cell Marque, CA, USA) [66]. The positive brown immune reactions of all sections were quantified using ImageJ software (NIH, Bethesda, MD, USA) [17].

Statistical analysis

The data collected were presented as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) test was carried out, followed by a post-hoc test to determine the significance of data among different (studied) groups, which was accomplished by the least significant differences (LSD) test. $P < 0.05$ were considered significant. Statistical analysis was conducted using SPSS software version 22.0 (IBM Corporation).

Results

Phytochemical and antioxidant activity of MCF

The phytochemical contents such as phenolic and flavonoid components were quantitively analyzed to estimate the chemical profile of bitter melon fruit supplement. The result of the phenolic test revealed that MCF presented a good source of phenolic contents with 15.74 ± 0.02 mg gallic acid equivalents (GAEs) per 1 g of the tablet sample. The analysis of the flavonoid contents of MCF revealed the presence of flavonoid contents with 4.29 ± 0.03 mg quercetin equivalents (QEs) per 1 g of the tablet sample. The DPPH radical scavenging activity was recorded in terms of % Inhibition. The results revealed that bitter melon fruit tablets displayed comparatively moderate antioxidant activity (72.44 ± 0.33%). Higher % Inhibition indicates better scavenging activity and antioxidant potential. The results of the present study suggested that bitter melon fruit supplement could be a good source of natural

antioxidants because of its phenolic and flavonoid contents, and its remarkable scavenging effects on DPPH.

Parasitological status

The present data after mono and dual-treatments (PZQ, MCF, and PZQ + MCF) revealed a significant ($P < 0.05$) reduction in the total number of the worms and ova count per gram (liver and intestine), worm reduction percent (44.4%, 40.8%, 100%, respectively), ova reduction (liver: 74.7%, 54.2%, 60.1%; intestine: 66.2%, 51.7%, 62.3%, respectively) (Table 1(A)), associated with a significant elevations in the count of dead ova in all treated groups (PZQ, MCF, and PZQ + MCF) and a significant difference was observed in mean numbers of immature eggs in hepatic and intestinal segments compared with infected control mice (Table 1(B)). Also, treatment with PZQ alone resulted in a higher reduction in ova count than that of MCF. On the other hand, dual treatment of MCF plus PZQ showed complete reduction of worm burden when compared to treatment with PZQ alone (Table 1(A)).

Ultrastructure morphological observation of adult male S. mansoni

Normal morphology of the male tegument worm with normal tubercles covered with large, numerous, and sharp spines, sensory organelles, and intertubercular ridges was obtained from the positive infected-mice without treatment (Fig. 1 A and B). The worms from the PZQ-treated group showed tegumental damage in the form of an erosion of the tubercles and a marked decrease in spines or even complete loss of them (Fig. 1 C and D). The worms from the infected-mice treated with MCF showed a distortion of tubercles, complete loss of spines, and loss of intertubercular ridges (Fig. 1 E and F). Moreover, dual treatment of MCF plus PZQ exhibited a complete loss of adult worm confirmed with that has already mentioned in the obvious worm burden (Table 1(A)). The worms from infected-mice without treatment showed normal ventral and oral suckers (Fig. 2A); anterior region of oral and ventral suckers was covered by numerous sharp spines with variable size (Fig. 2 B and C; respectively). In all treated group (PZQ or MCF), obvious deformity of oral and ventral suckers (Fig. 2 D and G), with obvious decrease in the number of spines in the area of oral and ventral suckers (Fig. 2 E and F; H and I, respectively).

Histological observations

H&E stain for illustrating thehistological changes of liver and intestine

Normal liver structure was observed in the control group, that contained conventional hepatocytes, separated by blood sinusoids without *S. mansoni* egg or inflammatory signs (Fig. 3A). While in the *S. mansoni* infected-mice, severe inflammatory process was observed in the form of trapped parasiticova in hepatic tissue; dilated hepatic sinusoids, cytoplasmic vacuolation, cellular infiltration, degenerated hepatocytes,necrotic area, and severe fibrocellular granuloma with a mean diameter of 158.57 ± 34.32 µm (Table 2 and Fig. 3 B and C). A moderate inflammatory process was observed in the *S. mansoni*-infected liver mice treated with PZQ, *S. mansoni* ova was mostly viable and some were already dead (Fig. 3D). The infected mice treated with MCF revealed a mild to a moderate inflammatory process with a reduction in the diameter of granulomas, and an increased number of binucleated hepatocytes indicating of cell regeneration in liver sections (Table 2 and Fig. 3E). The dual treatment (PZQ + MCF) revealed a remarkable improvement with an increased number of binucleated hepatocytes, and a reduction in the granuloma diameter with a slight inflammatory process in hepatic tissue (Table 2 and Fig. 3F). Similar morphological alterations in all treated groups were observed in the intestinal sections (Table 2 and Fig. 4). Normal well-organized intestinal tunics "mucosa with villi, submucosa, muscularis, and serosa" were observed in H&E sections ofthe uninfected control mice (Fig. 4A; Table 2). A chronic inflammatory response was observed around multiple fibrocelluar granuloma (69.46 ± 13.56 µm) in the mucosa and submucosa layers of the intestinal sections from the infected untreated mice, induced a distribution of the intestinal layers, damaged crypts and villi, a thick muscularis walls, inflammatory cell aggregations, necrotic area, and dilated blood vessels (Fig. 4 B and C; Table 2). The intestinal structure after the different treatments (PZQ, MCF, or PZQ + MCF) exhibited a remarkable amelioration of the intestinal injury with a significant decline ($P < 0.05$) in the diameter of the granuloma compared with the infected untreated group (Fig. 4D–F; Table 2). The greatest improvement was observed in mice dual-treated with both PZQ and MCF.

Masson trichrome stain for illustrating collagen fibers distributionin liver and intestine sections

The distribution percentage of collagen fibers in the liver and intestine of all test groups, as well as the quantified scoring system assessments of hepatic and intestinal fibrosis are presented in Table 2. Hepatic and intestinal sections of infected untreated mice revealed a severe fibrosis with much collagen fibers around hepatic and intestinal granuloma (Figs. 5A and 6A). Mono treatment with PZQ or MCF showed a moderate fibrosis with a slight decrease in the quantity of collagen fibres around granuloma (Table 2 and Figs. 5B, C and 6B, C) when compared to infected untreated mice. Dual treatment

Table 1 Effect of *Momordica charantia* fruit (MCF) and PZQ treatment on worm burden, ova count (A), and Oogram pattern (B) of *S. mansoni* infected mice

A: worm burden and ova count

Groups	Worm burden					Ova count			
	Male	Female	Couple	Total	Reduction (%)	Liver	Reduction (%)	Intestine	Reduction (%)
Infected mice (G2)	1.83 ± 0.75	0.00	7.17 ± 1.17	9.00 ± 1.10	–	6543.88 ± 703.49	–	8479.83 ± 468.27	–
PZQ (G3)	1.00 ± 0.00*	0.00	4.00 ± 0.89*	5.00 ± 0.89*	44.4%	1653.27 ± 305.98*	74.7%	2866.66 ± 485.80*	66.2%
MCF (G4)	1.17 ± 0.41*	0.00	4.17 ± 0.41*	5.33 ± 0.52*	40.8%	2999.94 ± 283.63*#	54.2%	4093.33 ± 174.36*#	51.7%
PZQ + MCF (G5)	0.00*#	0.00	0.00*#	0.0*#	100%	2613.33 ± 297.10*#	60.1%	3199.94 ± 369.38*	62.3%

B: Oogram pattern

Groups	Oogram pattern					
	Liver			Intestine		
	Mature eggs	Immature eggs	Dead eggs	Mature eggs	Immature eggs	Dead eggs
Infected mice (G2)	80.28 ± 0.93	15.28 ± 1.10	4.44 ± 0.40	73.17 ± 2.97	21.83 ± 3.09	5.00 ± 0.42
PZQ (G3)	12.11 ± 1.63*	10.17 ± 1.33*	77.55 ± 3.23*	19.94 ± 0.77*	7.00 ± 1.89*	73.05 ± 1.62*
MCF (G4)	45.11 ± 1.51*#	13.00 ± 1.67*#	41.89 ± 1.87*#	38.33 ± 1.85*#	9.11 ± 2.06*	52.55 ± 2.21*#
PZQ + MCF (G5)	32.50 ± 2.25 *#	13.66 ± 0.87*#	53.67 ± 1.98*#	19.61 ± 0.77*	8.22 ± 0.75*	72.16 ± 0.96*

The data are expressed as mean ± standard deviation (SD), ($n = 6$)

PZQ praziquantel, *MCF Momordica charantia* fruit

* Indicates a significant difference compared to infected control (G2) and # indicates significance against PZQ-treated group (G3)

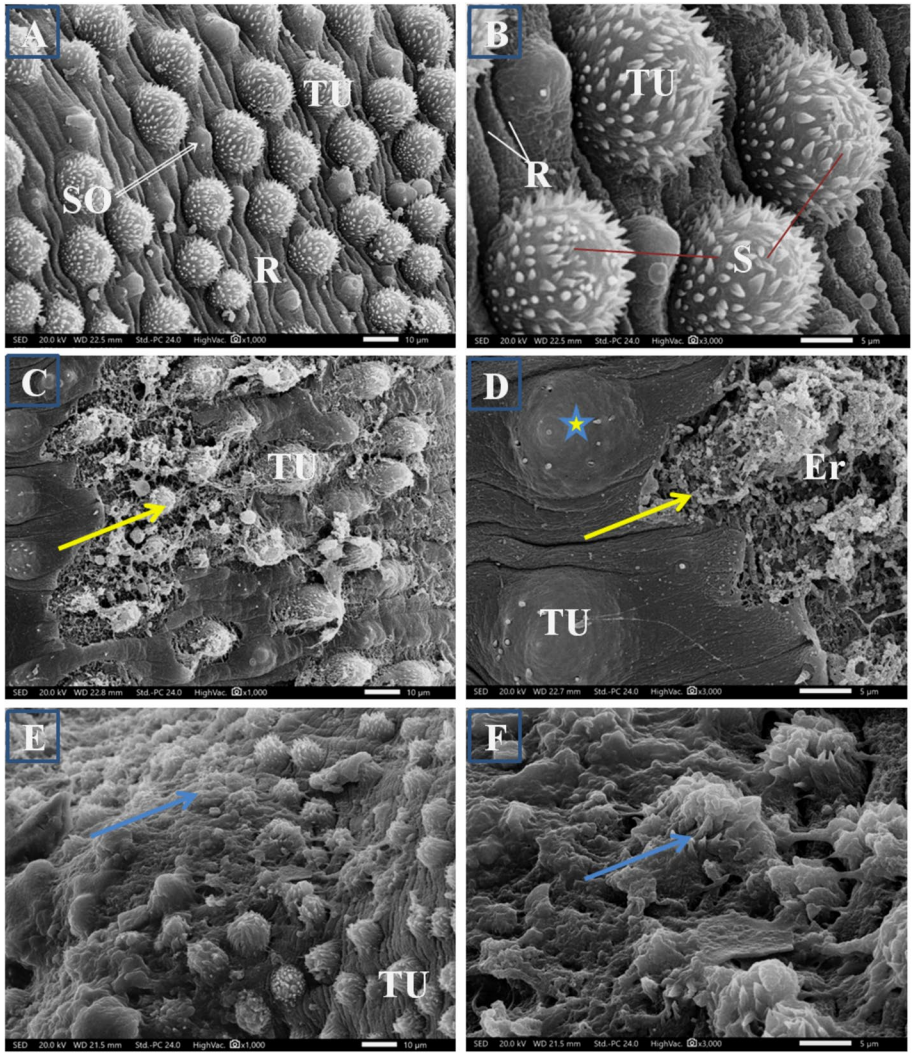


Fig. 1 Scanning electron micrographs of adult male *S. mansoni* worms from different groups ($n = 3$). **A**, **B** *S. mansoni* from an infected control mouse showing a normal morphology of the tegument, normal tubercles (TU), spines are sharp and numerous (S), sensory organelles (SO), and intertubercular ridges (R). **C**, **D** The worm from an infected-mouse treated with PZQ showing a marked destruction of the tegument (yellow arrows), erosion (Er) of the tubercles, and a marked decrease in spines or even a complete loss of spines (star). **E**, **F** The worm from an infected-mouse treated with MCF showing a distortion of tubercles, a complete loss of spines, and a loss of intertubercular ridges (blue arrows)

of PZQ plus MCF exhibited a significant reduction in fibrosis, as measured by the mean positive percentage of collagen in liver and intestine (2.04%, 0.77%, respectively) when compared to infected untreated mice (6.17%, 4.08%, respectively) (Figs. 5D and 6D).

Total IgG, IL-10, IFN-γ, NO, MDA, SOD, and CAT measurements

In Tables 3 and 4, the results of IL-10, total IgG, IFN-γ, MDA, and NO showed a higher level in the infected-mice, accompanied by a significant reduction in SOD and CAT activity compared with the normal control group. PZQ treatment significantly increased total IgG level, IFN-γ, NO, and these values were the highest compared to all other groups, accompanied by a significant reduction in MDA and IL-10. However, treatment with MCF alone resulted in a significant reduction in the level of IFN-γ and NO accompanied by a significant elevation in the IL-10 level as compared to PZQ-treated group. Oral administration of MCF alone enhanced NO production with a significant increase compared to the infected-untreated mice. In addition, oral administration of (PZQ + MCF) slightly ameliorated the NO level compared to PZQ-treated mice. All the treated groups demonstrated a

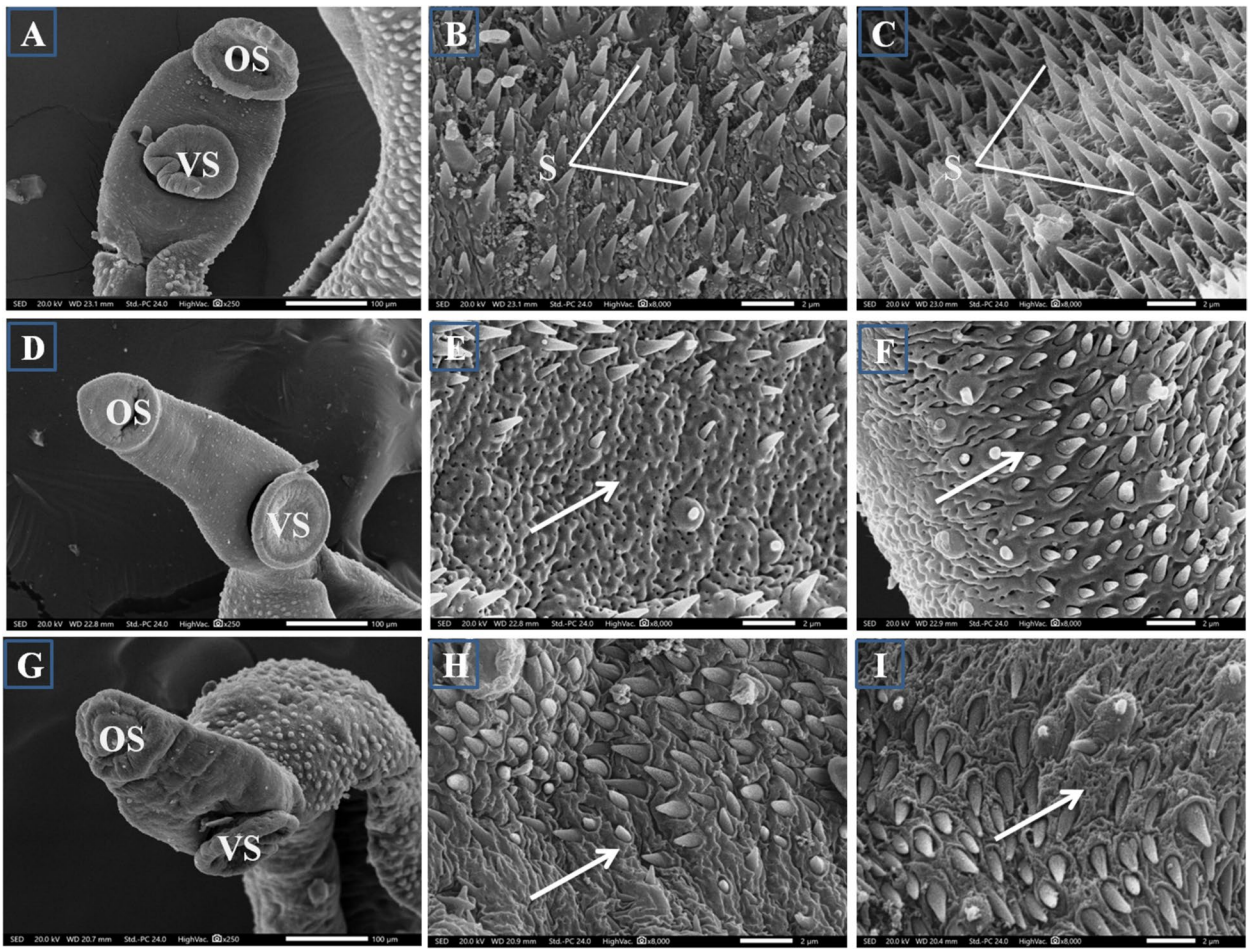


Fig. 2 Scanning electron micrographs of adult male *S. mansoni* worms displaying oral and ventral suckers from different groups ($n = 3$). **A**–**C** Worm from an infected control mouse showing (**A**) a normal morphology of an oral sucker (OS) and a ventral sucker (VS); **B** a normal anterior region of an oral sucker with numerous sharp spines (S); and **C** a normal anterior region of a ventral sucker with numerous sharp spines (S). **D**–**F** Worm from an infected mouse treated with PZQ showing (D) abnormal oral and ventral suckers; **E** an anterior region of an oral sucker with a marked decrease in spines (arrow); and **F** an anterior region of a ventral sucker with a marked decrease in spines (arrow). **G**–**I** Worm from an infected mouse treated with MCF displaying (**G**) oral and ventral suckers which loss their normal structure; **H** an anterior region of an oral sucker with a marked disturbance in the direction of spines, and a decrease in the number of spines (arrow); and **I** an anterior region of a ventral sucker with a marked disturbance in the direction of spines, and a decrease in the number of spines (arrow)

significant increases in SOD and CAT activity compared to the infected control mice.

Cellular immune response changes

In this study, to examine cellular immune response changes, the FACS flow cytometer was utilized to estimate the $CD4^+$ and $CD8^+$ cells in the blood. On the other hand, immunohistochemistry was utilized to demonstrate the $CD3^+$ and $CD20^+$ cells in the liver and intestinal tissues.

$CD4^+$ & $CD8^+$ cells detection in the blood

In *S. mansoni*-infected mice, results showed a significant decrease in the $CD4^+$ and $CD8^+$ cells in the blood (Table 5) when compared with the normal control animals. Mono treatment with PZQ or MCF alone led to a significant elevation in $CD8^+$ cells and $CD4^+$ cells in the blood compared with the infected mice group (Table 5). After oral administration of PZQ + MCF, no significant differences were detected in the $CD4^+$ cells and $CD8^+$ cells in the blood compared to infected control mice (Table 5).

Immunohistochemical examinations

$CD3^+$ and $CD20^+$ antibodies are commonly used to diagnose infiltration of T or B cells in the tissue infected by *S. mansoni*. In the current study, immunohistochemistry was utilized to demonstrate the $CD3^+$

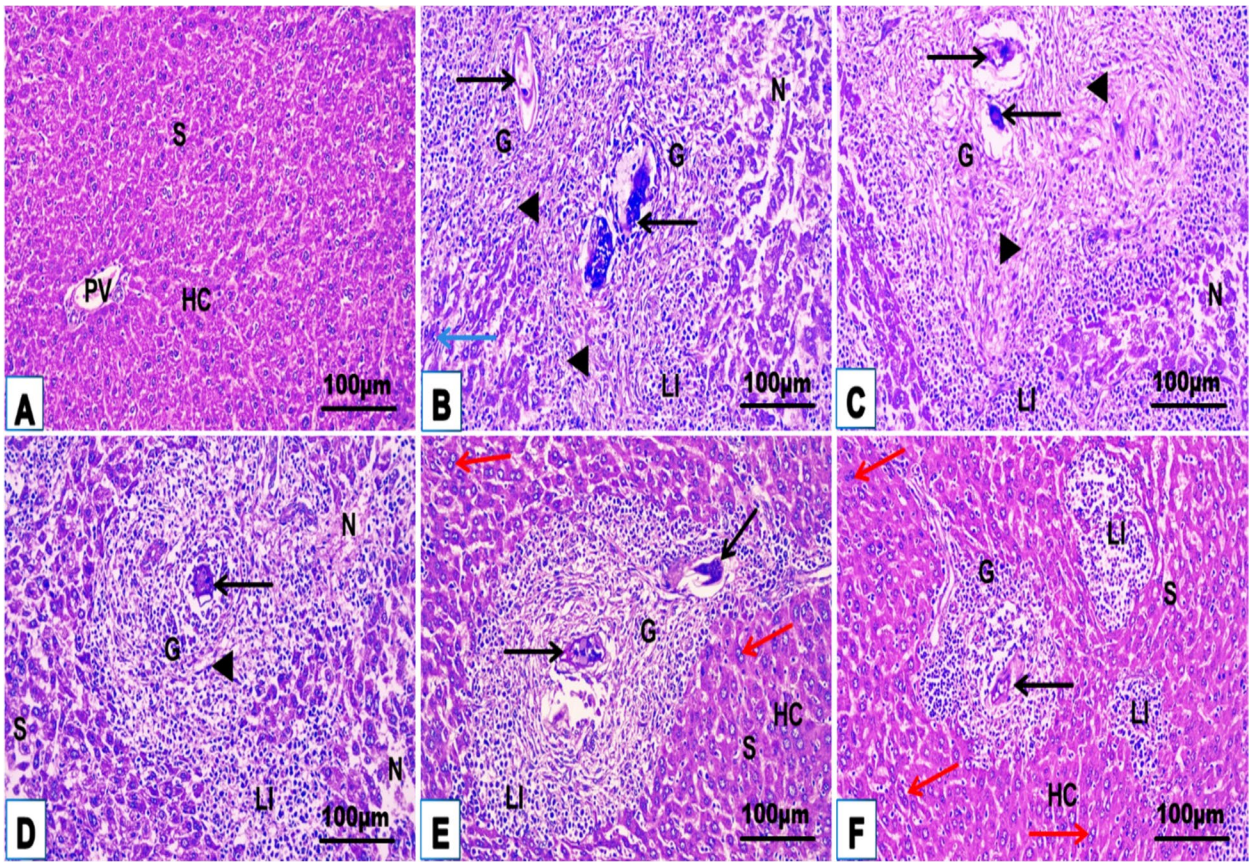


Fig. 3 Representative photographs of liver sections from mice of all groups stained with H&E of **A** control group, **B**, **C** infected group showing large fibrocellular granulomas, **D** infected mice treated with PZQ displaying a decrease of the granuloma diameter, **E** infected mice treated with MCF showing a reduction in granuloma diameter, **F** infected mice treated by both PZQ and MCF displaying a noticeable improvement with a significant decrease of granuloma diameter. *CV* central vein, *G* granuloma, *HC* hepatocytes, *Li* leucocytic infiltration, *N* necrosis, *PV* portal vein, *S* sinusoids; black arrows: *S. mansoni* ova, red arrows: binucleated hepatocytes, arrow heads: fibers of granuloma, H&E stain, ×20 magnification, bar = 100 µm

Table 2 Effect of MCF and PZQ treatment on hepatic granuloma, positive expression of collagen fibers, and fibrosis score

Group	Liver			Intestine		
	Granuloma diameter (µm)	Collagen fiber %	Ishak scoring	Granuloma diameter (µm)	Collagen fiber %	Fibrosis Score
Infected mice (G2)	158.57 ± 34.32	6.17 ± 2.42	4.60 ± 0.51	69.46 ± 13.56	4.08 ± 0.94	2.80 ± 0.42
PZQ (G3)	84.83 ± 16.16*	3.38 ± 0.92*	3.50 ± 0.70*	53.12 ± 9.67*	2.52 ± 0.64*	1.90 ± 0.56*
MCF (G4)	64.58 ± 10.78$^{*\#}$	3.88 ± 1.78*	3.10 ± 0.73$^{*\#}$	46.24 ± 5.61$^{*\#}$	2.59 ± 0.79*	1.70 ± 0.67$^{*\#}$
PZQ + MCF (G5)	60.59 ± 8.00$^{*\#}$	2.04 ± 0.59*	1.9 ± 0.56$^{*\#}$	35.77 ± 7.10$^{*\#}$	0.77 ± 0.21$^{*\#}$	0.80 ± 0.63$^{*\#}$

The data are expressed as mean ± standard deviation (SD), ($n = 5$)

PZQ Praziquantel, *MCF Momordica charantia* fruit

* Indicates a significant difference compared to the infected control (G2), and $^{\#}$ indicates significance against PZQ-treated group (G3)

and CD20^{+} cells in the liver and intestinal sections. In the infected untreated mice, there was a significant increase in the positive brownish color of the immune-reacted cells CD3^{+} and CD20^{+} (Table 6, Figs. 7, 8, 9 and 10). Mono treatment of infected mice with PZQ or MCF showed a decrease in the expression of CD3^{+} and CD20^{+} in liver and intestinal tissues compared to the infected untreated mice (Table 6 and Figs. 7, 8, 9 and 10). The dual treatment of PZQ and MCF exhibited a mild expression of CD3^{+} and CD20^{+} compared to mice infected with *S. mansoni* without any treatment (Figs. 7, 8, 9 and 10).

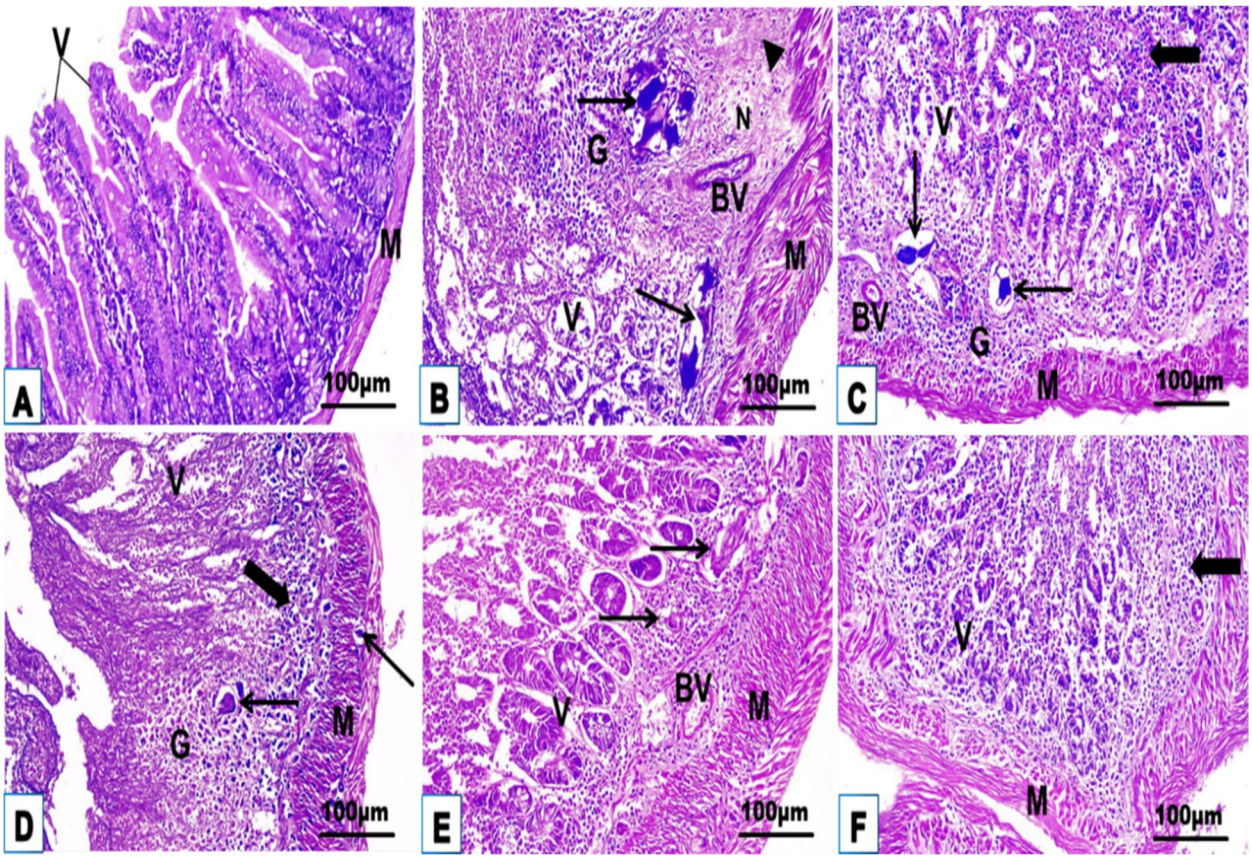


Fig. 4 Representative photographs of intestinal sections from mice of all groups stained with H&E of **A** control group, **B**, **C** infected group showing large multiple granulomas, **D** infected group treated with PZQ displaying a decreased diameter of granuloma, **E** infected group treated with MCF showing a reduction in granuloma diameter, **F** infected group dual-treated by PZQ and MCF showing a significant improvement with a reduction of granuloma. *BV* blood vessel, *G* granuloma, *M* muscularis, *N* necrosis, *V* villi; thin arrows: *S. mansoni* ova, thick arrows: aggregation of inflammatory cells, arrow head: fibers of granuloma, H&E stain, ×20 magnification, bar = 100 µm

Discussion

Schistosomiasis is a severe tropical parasitic disease that causes a variety of clinical manifestations in humans. The Schistosomiasis treatment remains dependent on PZQ alone, but PZQ cannot repair tissue damage, and cannot prevent re-infection. There are several researches for effective antischistosomal agents with minimal side effects to be used as adjuvants to increase the effect of PZQ [38, 72]. Thus the current study was performed to evaluate the therapeutic effects of MCF alone or in combination with PZQ on *S. mansoni* infected-mice. The extracts of various plant parts of *M. charantia* including the leaf, fruit, and seeds had been investigated in treatment of different parasitic infection [68].

The current phytochemical test results revealed that MCF contains sufficient phenolic and flavonoid contents that act as free radical scavengers, so MCF supplement could be a powerful source of natural antioxidants. MCF supplements could be effective in inhibiting the harmful effects of oxidative stress and may be an alternative therapy to cure various harmful diseases due to their phytochemical contents. *M. charantia* contains multiple flavonoids, saponins, phenolic compounds, terpenoids, tannins, protein, alkaloids, steroids, and carbohydrate, which are used to remove the harmful action of free radicals after parasitic infection [19].

The current result displays a significant increase in the percentage of worm reduction (40.8%) with a significant elevation in the percentage of dead ova, and significant changes ($P < 0.05$) of the oogram pattern of liver and intestine in MCF treated mice. These results go hand in hand with that of Williams et al. [82], who reported that tannins as functional ingredients of *M. charantia* showed an antiparasitic effect by decreasing a migratory ability and survival of hatched larvae, reducing the worm burden, and causing the damage of the digestive tissues of worms. Furthermore, tannins inhibited energy generation of worms by uncoupling the oxidation phosphorylation and bind to glycoproteins on the cuticles of the worms leading to death [82]. In the present study,

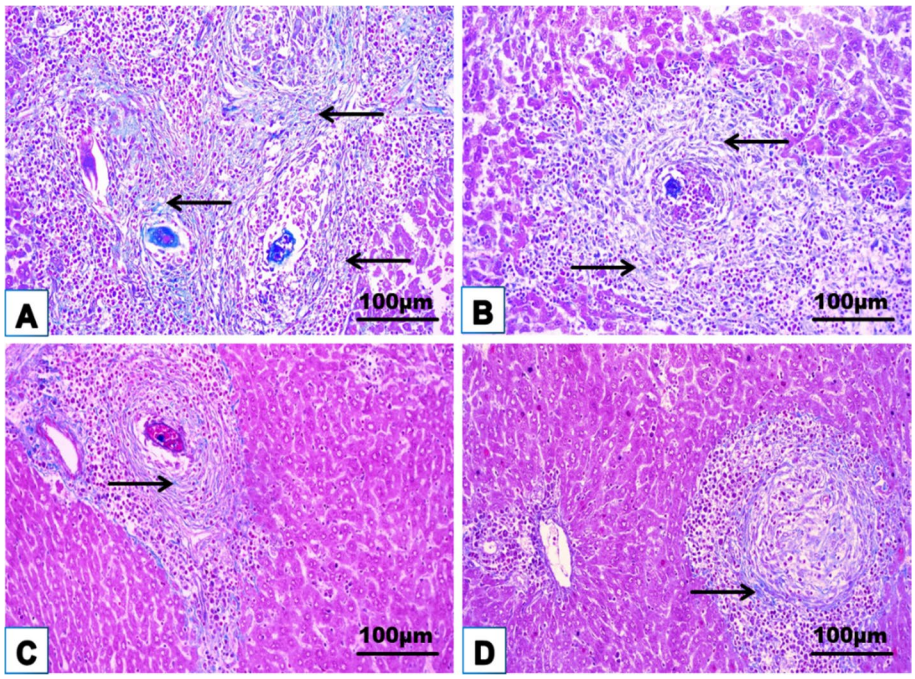


Fig. 5 Representative photomicrographs of liver sections stained by Masson trichrome-illustrated collagen fibers distribution (arrows) of **A** infected group with a marked increase in collagen fibers, **B** infected mice treated with PZQ revealing a moderate fibrosis, **C** mono treatment with MCF exhibiting aslight deposition of collagen fibers in granuloma, **D** dual treatment (PZQ and MCF) revealing a marked reduction in collagen fibers in granuloma. Masson trichrome stain, ×20 magnification, bar = 100 µm

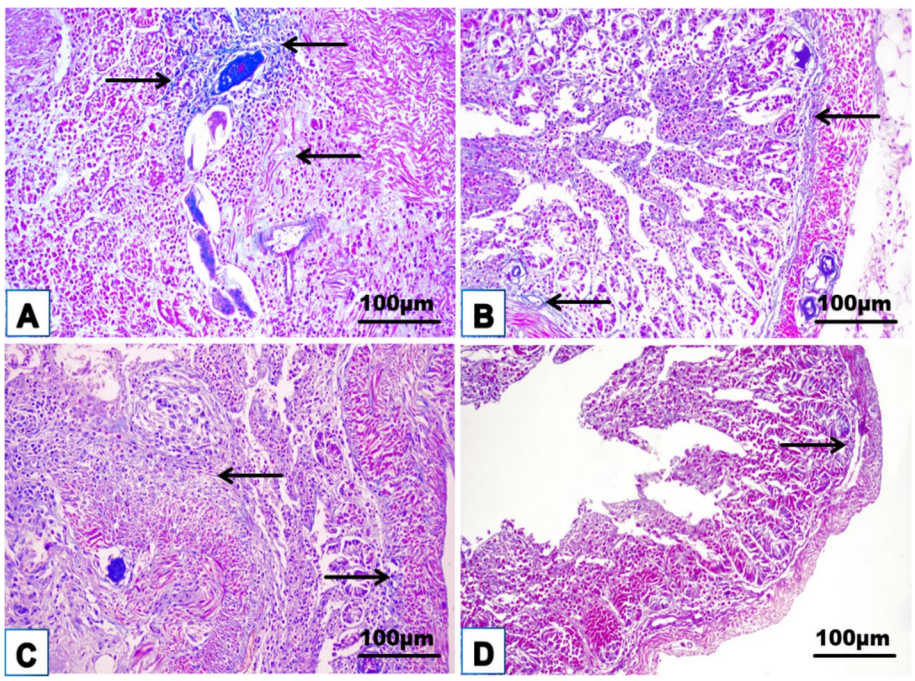


Fig. 6 Representative photomicrographs of intestinal sections stained by Masson trichrome-illustrated collagen fibers distribution (arrows) of **A** infected group with a marked increase in collagen fibers, **B** infected mice treated with PZQ revealing a moderate fibrosis, **C** mono treatment with MCF exhibiting a slight depositionof collagen fibers in granuloma, **D** dual treatment (PZQ and MCF) revealinga marked reduction in collagen fibers in granuloma. Masson trichrome stain, ×20 magnification, bar = 100 µm

Table 3 Effect of MCF and PZQ treatment on total IgG, IL-10, and IFN-γ in serum samples of different groups

Groups	Immune parameters		
	Total IgG (ng/ml)	IL-10 (pg/ml)	IFN-γ (pg/ml)
Normal control(G1)	26.36 ± 2.00	25.58 ± 3.41	224.68 ± 5.12
Infected control(G2)	159.5 ± 2.25$^{\$}$	66.90 ± 4.31$^{\$}$	400.90 ± 14.67$^{\$}$
PZQ(G3)	170.26 ± 2.84*	50.94 ± 3.01*	633.10 ± 19.98*
MCF(G4)	160.90 ± 2.23$^{\#}$	76.25 ± 2.78$^{*\#}$	365.40 ± 4.55$^{*\#}$
PZQ + MCF(G5)	168.94 ± 4.16*	62.78 ± 4.11$^{\#}$	406.55 ± 13.35$^{\#}$

The data are expressed as mean ± standard deviation (SD), ($n = 5$)

IgG immunoglobulin G, *IL*−10 interleukin 10, *IFN*-γ interferon gamma, *PZQ* Praziquantel, *MCF Momordica charantia* fruit

* Indicates a significance ($P < 0.05$) against the infected control, $^{\#}$ indicates a significance against PZQ-treated mice, and $^{\$}$ indicates a significance against the normal healthy control

mono treatment with PZQ led to more effective results than MCF alone, while dual treatment of MCF and PZQ resulted in a complete reduction of worm burden in comparison to infected-mice treated with PZQ alone. Treatment of leaves extracts derived from *M. charantia* against *Fasciola hepatica* were significantly inhibited the hatching of eggs of *F. hepatica* in vitro at 12.5 mg/ml after 12 days of exposure [67]. Sen et al. [71] reported that methanolic extract of *M. charantia* fruit had a potential anthelmintic effect against *Eisenia foetida* where its administration at150 mg/ml showed paralysis and death of parasites.

The tegument of *S. mansoni* worm plays an important role in nutrient absorption, proliferation, metabolism, secretory functions, and parasite protection against the host immune system [28, 77]. In addition, worm tegument is considered to be a major target for antischistosomal drugs [46]. The alterations of the tegument can be used to estimate the antischistosomal activity of the drugs [27]. Since bitter melon caused a significant reduction in the worm burden, the current work investigated

Table 5 Effect of MCF and PZQ treatment on immune cell markers of the different groups

Groups	Blood	
	CD4 +	CD8 +
Normal control (G1)	61.03 ± 1.59	38.00 ± 0.62
Infected control (G2)	41.58 ± 1.37 $	34.78 ± 3.79
PZQ (G3)	51.30 ± 2.91*	46.60 ± 2.68*
MCF (G4)	51.18 ± 3.31*	49.68 ± 0.54*
PZQ + MCF (G5)	39.53 ± 0.45 #	36.43 ± 2.93 #

The data are expressed as mean ± standard deviation (SD), ($n = 3$)

CD cluster of differentiation, *PZQ* Praziquantel, *MCF Momordica charantia* fruit

* Indicates a significance ($P < 0.05$) against the infected control, $^{\#}$ indicates a significance against PZQ-treated mice, and $^{\$}$ indicates a significance against the normal control

Table 6 Effect of MCF and PZQ treatment on the percentages (%) of $CD3^{+}$ and $CD20^{+}$ expression in hepatic and intestinal sections

Groups	Tissue			
	Liver		Intestine	
	CD3 + %	CD20 + %	CD3 + %	CD20 + %
Normal control (G1)	ND	ND	ND	ND
Infected control (G2)	7.25 ± 0.83	11.21 ± 2.27	7.66 ± 1.59	8.42 ± 1.52
PZQ (G3)	2.14 ± 0.79 *	3.26 ± 1.13*	2.37 ± 0.79 *	2.96 ± 0.77*
MCF (G4)	1.44 ± 0.31*#	4.39 ± 1.16*	2.63 ± 0.70 *	2.21 ± 0.72*
PZQ + MCF (G5)	1.37 ± 0.35*#	2.14 ± 0.37*	2.04 ± 0.83 *	2.04 ± 0.86*

The data are expressed as mean ± standard deviation (SD), ($n = 5$)

CD cluster of differentiation, *PZQ* Praziquantel, *MCF Momordica charantia* fruit, *ND* not detected

* Indicates a significance ($P < 0.05$) against the infected control, $^{\#}$ indicates a significance against PZQ-treated mice, and $^{\$}$ indicates a significance against the normal control

Table 4 Antioxidant–oxidative status of different experimental groups

Groups	Antioxidant parameter			
	NO (μmol/L)	SOD (U/ml)	CAT (U/ml)	MDA (nmol/ml)
Normal control (G1)	4.48 ± 0.44	77.33 ± 2.37	24.48 ± 1.78	4.86 ± 0.68
Infected control (G2)	8.10 ± 0.65$^{\$}$	64.36 ± 1.30$^{\$}$	15.64 ± 1.47$^{\$}$	10.20 ± 1.12$^{\$}$
PZQ (G3)	13.44 ± 0.50*	68.55 ± 1.65*	24.14 ± 0.58*	8.90 ± 0.71*
MCF (G4)	9.90 ± 0.70$^{*\#}$	70.96 ± 1.03*	25.72 ± 1.18*	8.98 ± 0.29*
PZQ + MCF (G5)	11.56 ± 0.44$^{*\#}$	77.92 ± 2.73$^{*\#}$	24.06 ± 0.15*	8.40 ± 0.43*

The data are expressed as mean ± standard deviation (SD), ($n = 5$)

NO nitric oxide, *SOD* superoxide dismutase, *CAT* catalase, *MDA* malondialdehyde, *PZQ* Praziquantel, *MCF Momordica charantia* fruit

* Indicates a significance ($P < 0.05$) against the infected control, $^{\#}$ indicates a significance against PZQ-treated mice, and $^{\$}$ indicates a significance against normal healthy control

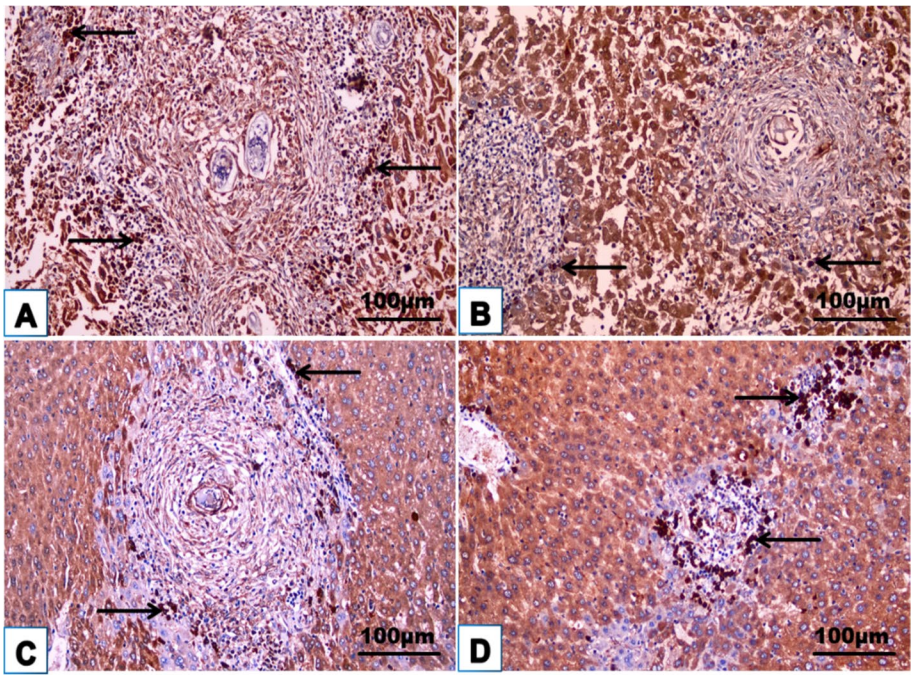


Fig. 7 Representative photomicrographs of the immunohistochemical $CD3^+$ expression (arrows) in the hepatic sections of the infected mice **A** without treatment, **B** treated with PZQ, **C** treated with MCF, and **D** treated with PZQ and MCF. IHC, × 20 magnification, bar = 100 µm

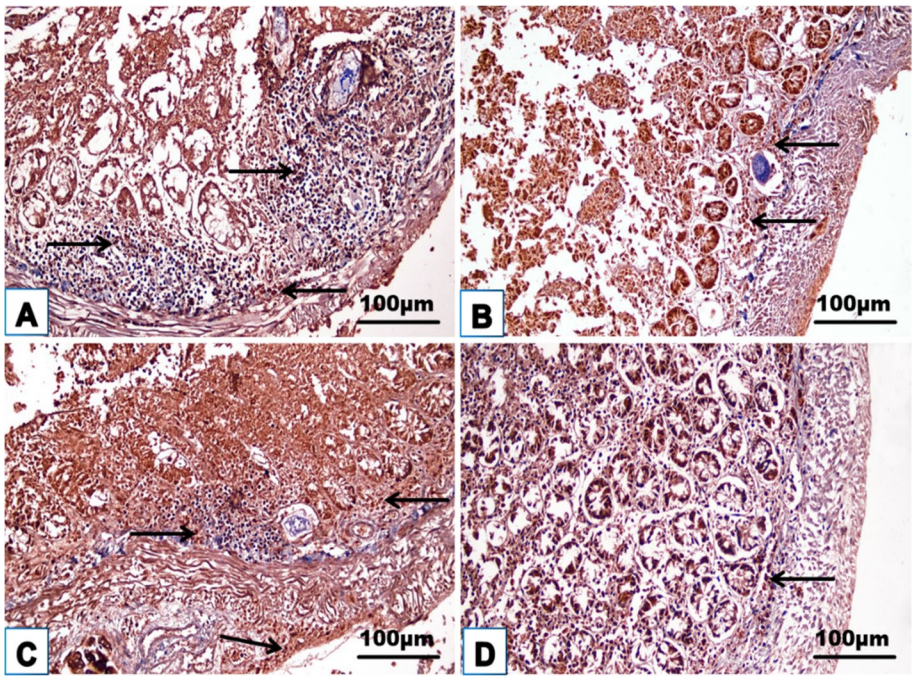


Fig. 8 Representative photomicrographs of the immunohistochemical $CD3^+$ expression (arrows) in the intestinal sections of the infected mice **A** without treatment, **B** treated with PZQ, **C** treated with MCF, and **D** treated with PZQ and MCF. IHC, × 20 magnification, bar = 100 µm

the effect of bitter melon fruit supplement on *S. mansoni* worm of the infected mice. The ultra-structural changes in the tegument, morphology of the oral and ventral suckers of adult male worms isolated from the MCF-treated mice were studied using SEM. Treatment with MCF showed a distortion of tubercles, a complete loss of

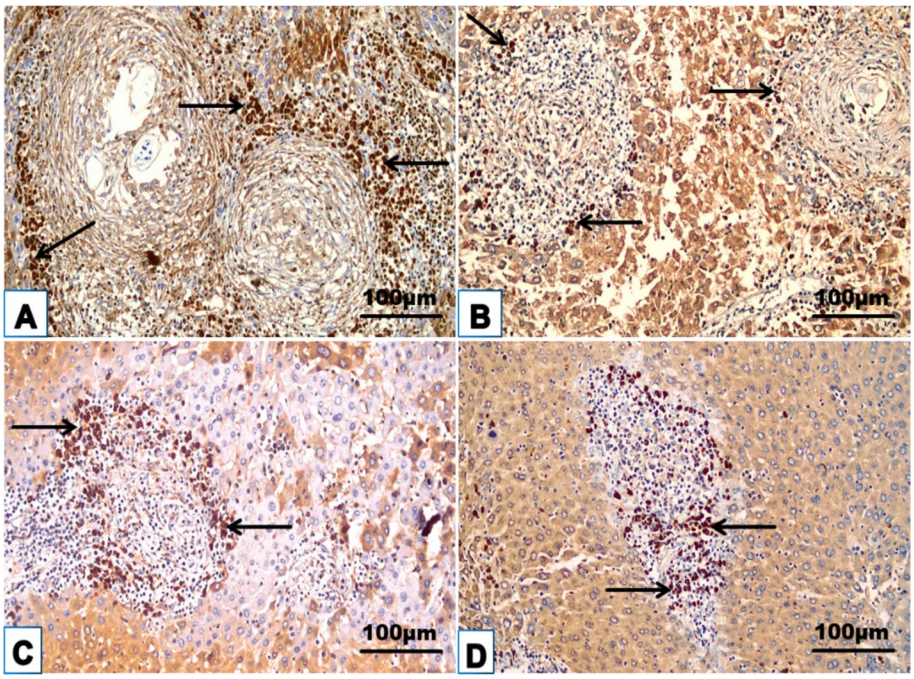


Fig. 9 Representative photomicrographs of the immunohistochemical $CD20^{+}$ expression (arrows) in the hepatic sections of the infected mice **A** without treatment, **B** treated with PZQ, **C** treated with MCF, and **D** treated with PZQ and MCF. IHC, × 20 magnification, bar = 100 µm

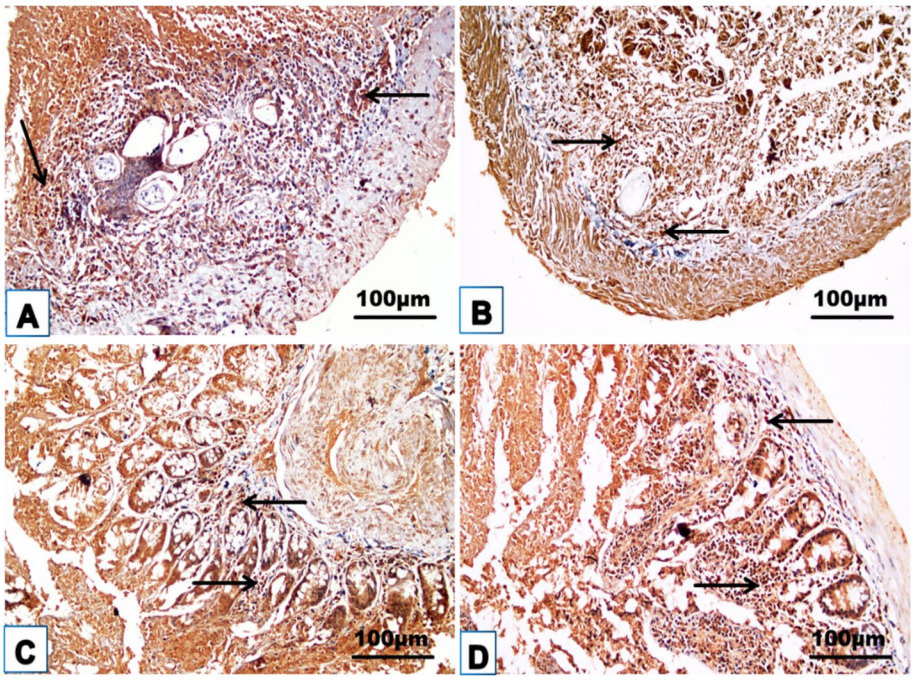


Fig.10 Representative photomicrographs of the immunohistochemical $CD20^{+}$ expression ((arrows) in the intestinal sections of the infected mice **A** without treatment, **B** treated with PZQ, **C** treated with MCF, and **D** treated with PZQ and MCF. IHC, × 20 magnification, bar = 100 µm

spines, a loss of intertubercular ridges, and a marked disturbance in the direction of spines in the anterior region of the oral and ventral suckers. These results indicated that MCF can have an anthelmintic effect by destroying the surface tegument of the adult worm. Mada et al. [51] and de Oliveira et al. [19] attributed that to the presence

of functional ingredients involving saponins. Saponins affected the permeability of the cell membrane of worms and caused disintegration and vacuolization of tegument [8, 57]. Also, SEM of worms of PZQ-treated group in the present work exhibited pronounced tegumental damage of *S. mansoni* worm in the form of a marked destruction of the tegument with an erosion of the tubercles and a marked decrease in spines or even complete loss of spines. Moreover, a marked ulceration on the outer surface was detected. These results were in parallel with several studies in vitro or in vivo [21, 24] which reported that PZQ showed a pronounced tegumental damage of *S. mansoni* male and female worms in the form of rupture of the tubercles, loss of spines in wide areas, and some teguments showed severe erosion.

The histological alterations in the liver and intestinal tissues of *S. mansoni*-infected untreated or treated mice were the focus of the current investigation. In the *S. mansoni*-infected mice, liver and intestine sections showed severe inflammatory infiltration around trapped *S. mansoni* ova and worms. These alterations were in agreement with Saad El-Din et al. [69] who mentioned that the liver of the *S. mansoni*-infected group without treatment showed granulomatous reaction surrounded by inflammatory cells or fibrous connective tissue. There was a significant difference between infected mice and infected groups treated with PZQ, MCF, or both. These abnormalities in the liver and intestine of the infected mice were improved following mono or dual therapy. In the present investigation, infected mice treated with PZQ and MCF resulted in a reduction in granuloma diameter, collagen fiber deposition, and a mild to moderate inflammatory process. The current PZQ results were in parallel with Madbouly et al. [52] who found that oral administration of 500 mg/kg PZQ for two consecutive days, 42 days post-infection revealed medium-sized fibrocellular granuloma with degenerated egg. This reduction in tissue granuloma may be attributed to the recorded reduction in total worm burden. The relation between worm burden, egg load, and granuloma formation were studied and was proved by Botros et al. [10]. Sagor et al. [70] reported that fresh ucche *M. charantia* supplementation prevented fibrosis and hepatic damage in CCl4-treated rats. Interestingly, dual treatment revealed a remarkable decrease in granuloma diameter with a mild inflammatory process, and a significant decrease in collagen fibre deposition.

Immune response has a critical role in *Schistosoma* infection. Once infected with *Schistosoma* parasite, the initial response in the plasma and infected tissues is characterized by type-1 inflammation, that is drived by IL-12, IL-1, IFN-γ, and tumor necrosis factor-α [80]. Immune response is subsequently choked during chronic schistosomiasis by the $CD4^+$ T helper 2 response, which is triggered by antigens secreted by ova and is driven by IL-13, IL-10, IL-9, IL-6, IL-5, and IL-4 [43]. The IL-10 cytokine plays an important role in disease progression by encouraging inflammation through down regulation of the Th1 response but also preventing severe disease during the Th2 response [54]. The current study investigated the modulation of immune response against Schistosomiasis by estimating of total IgG, IL-10 (Th2 cytokine), and IFN-γ (Th1 cytokine) under the influence of PZQ in mice experimentally infected with *S. mansoni*. IL-10, total IgG, and IFN-γ levels showed a significant increase in infected untreated mice compared to the healthy control group. This may be due to the lack of hepatic clearance function which results in elevated serum cytokine levels. Mono treatment of infected-mice with PZQ reversed the immune response from Th2 to Th1 by a significantly higher increase in IFN-γ levels as shown, and decreased IL-10 compared with infected untreated mice. This result is in agreement with Sharaf et al. [73], who reported that treatment with PZQ in murine models caused a significant increase in IFN-γ levels. On the other hand, other studies revealed a very highly significant increase in the level of IFN-γ and a significant decrease in IL-10 under the effect of PZQ [23, 52]. Mono treatment of infected mice with MCF alone revealed a significant decrease in IFN-γ levels and a significant increase in IL-10 when compared with infected untreated mice while dual treatment PZQ accompanied by MCF showed a very highly significant decrease in IFN-γ levels with a very slight increase inIL-10 levels compared to PZQ-treated mice. This data comes in agreement with Ali et al. [4] who reported that treatment of *M. charantia*to *Plasmodium berghei* infected mice caused a significant decrease in IFN-γ and significantly increased IL-10 level. The present study showed that dual treatment of PZQ and MCF may cause a shift from Th2 to Th1.

The current data revealed that infection with *S. mansoni* resulted in an increasing of oxidative stress markers (NO and MDA), and the depletion of antioxidant enzymes (SOD and CAT). All treatment (PZQ, MCF, PZQ + MCF) demonstrated a significant increase in SOD and CAT activities, with a significant decrease in MDA compared with the infected untreated group. Moreover, there was a restoration of nearly normal values associated with a reversal action of fibrosis and a reduction in the granuloma diameter in mice treated with PZQ plus MCF. In agreement with that outcome, oral administration of *M. charantia* fruit extract in diabetic rats revealed a significant increase in antioxidant enzymes (SOD, CAT, and GSH) [1]. Also, these results were in parallel with Wang et al. [79] who reported that oral administration of polysaccharides from *M. charantia* juice improved

antioxidant ability by increasing SOD and reducing MDA in diabetic mice model. The current data recorded a significant increase NO in the infected untreated mice as compared to the healthy control group. This result comes in agreement with Ibrahim et al. [38] and Nofal et al. [63] who reported that Schistosomiasis caused a significant increase in the level of NO compared with the control group. Also, this study illustrated that PZQ-treated mice alone, MCF mono treatment, or dual treatment (PZQ + MCF) recorded a significant increase in NO level when compared with infected control mice. The previous study found that an elevation in NO level in hepatic tissue of PZQ-treated animals could attributed to the activation of the immune system, which increase the level of IFN-γ that can activate macrophages to produce NO and other inflammatory mediators [63]. In addition, the results of MCF comes in agreement with Abas et al. [1] who reported that oral administration of *M. charantia* fruit extract revealed significant increase in aortic tissue NO level and decrease in MDA in type 1 diabetic rat model. This in turn may generate an antifibrogenic effect on the *S. mansoni* granuloma and decrease granuloma diameter.

The protective mechanisms against schistosomiasis are concentrated on $CD4^+$ T cells and antibody responses [9]. Granuloma formation and fibrosis in murine schistosomiasis is a manifestation of CD4 cell-mediated immunity against soluble schistosomal egg antigen [49]. Granulomas are then gradually downregulated, largely by $CD8^+$ lymphocytes [26]. The current data revealed a significant elevation in the $CD4^+$ and $CD8^+$ cells in mono treatment with PZQ or MCF. These results go hand in hand with those of Manabe et al. [53], who showed that the dietary intake of *M. charantia* significantly increased the percentage of $CD4^+$ cells in the spleen. Dual treatment with PZQ + MCF showed no significant differences in these cell percentages compared to infected control mice which indicates antagonistic influence of the examined agents after combination which might be not only minimizes the immune response to the parasite infection but also reduce the inflammatory status after the combination therapy.

The granuloma of *Schistosoma* is formed of collagen fibers and different cell types including T and B cells, macrophages, eosinophils, and neutrophils that react with each other in a highly complex fashion [48]. Granuloma is formed by the mixture of $CD68^+$ histiocytes/dendritic cells, $CD20^+$ B cells, and $CD3^+$ T cells [37]. The histological and immunohistochemical examination of all treated mice with MCF, PZQ, or PZQ + MCF revealed a significant decrease in both granuloma diameters, accompanied by a reduction in $CD3^+$ and $CD20^+$ cells compared to the infected control mice. Following the present observation, the infiltration of fibroblasts into the worm granuloma sites could attract lymphocyte cells as well as forming collagen; the antifibrogenic effect of MCF may clarify the reduction in the granuloma diameter and cellularity.

Conclusion

The current study is the first of its kind to prove that administration of MCF could ameliorate *S. mansoni* infected-mice by enhancing immune response, increasing antioxidant levels, and reducing collagen deposition. Other studies are needed to explore the underlying mechanisms. This study highlighted the effects of MCF on Schistosomiasis, and encourages research in future to use MCF as a supplement to treat fibrosis arising due to Schistosomiasis.

Abbreviations

MCF	*Momordica charantia* Fruit
SEM	Scanning electron microscopy
PZQ	Praziquantel
IFN-γ	Interferon-gamma
IgG	Immunoglobulin G
ELISA	Enzyme-linked immunosorbent assays
NO	Nitric oxide
CAT	Catalase
SOD	Superoxide dismutase
FACS	Fluorescence- activated cell sorting
LSD	Least significant differences
GAEs	Gallic acid equivalents
QEs	Quercetin equivalents

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Authors' contributions

AMS revised the results and shared in manuscript writing and editing. HMI established the concept of the study and analyzed data. AHM constructed the idea, shared in interpreting the results, and revised the manuscript. AEN provided the study design and conducted data analysis. AMS and HMI applied clinical studies, collected data, and shared in writing the manuscript. AMS collected data, analyzed results and prepared manuscript. All authors read, revised and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Prior to the commencement of the study, each participant completed a written consent that was authorized by Institutional Animal Ethical Committee, Menoufia University, Egypt. Additionally, the Institutional Review Board was obtained [Approval ID: MUFS/S/Pa/1/22].

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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