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RESEARCH ARTICLE

Potential antischistosomal effect of *Phoenix dactylifera* seed extract in *Schistosoma mansoni*-infected mice.

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ABSTRACT

Background: Schistosomiasis is a parasitic disease that affects humans and animals. Praziquantel (PZQ) is the standard treatment but lacks anti-fibrotic effects in *Schistosoma mansoni*-infected patients. *Phoenix dactylifera* (date) seeds have attracted interest in biomedical applications. **Aim:** This study evaluated the effectiveness of anti-fibrotic and anti-schistosomal properties of *P. dactylifera* seeds extract (PDSE) in a murine model. **Materials and Methods:** Fifty male CD1 mice (22 ± 3 g) were divided into five groups (n = 10): Group 1 (Gp1) served as a negative control. Gp2, Gp3, Gp4, and Gp5 were infected with 60–80 *S. mansoni* cercariae via tail immersion. After one month, Gp3 received PZQ (500 mg/kg) orally for two consecutive days. Gp4 was treated with PDSE (100 mg/kg) orally for 15 days, and Gp5 received PZQ followed by PDSE at the same doses. Parasitological, biochemical, and histological parameters were assessed. **Results:** PZQ treatment significantly reduced worm burden but had limited effects on granuloma formation. Treatments with PDSE and PZQ/PDSE considerably decreased the size of granulomas and reduced the number of worms and eggs in intestinal and hepatic tissues. Histopathological and biochemical analyses demonstrated that PDSE and PZQ/PDSE reduced the changes brought on by *S. mansoni* infection. **Conclusion:** Whether taken alone or in conjunction with PZQ, PDSE collectively showed anti-schistosomal potential by drastically lowering egg deposition and having an anti-fibrotic effect on granulomatous inflammation.

Keywords: Anti-fibrotic, Anti-Schistosomal, Infected mice, *Phoenix dactylifera*, Seeds extract, *Schistosoma mansoni*, Granuloma,

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INTRODUCTION

The parasite *Schistosoma sp* can infect humans and other vertebrates in a variety of ways (Rossi et al., 2024). Human infections are most frequently caused by *S. mansoni* and *S. haematobium* (Tabo et al., 2025). It is specifically the *S. mansoni* parasite that causes serious health issues; for example, the persistent infection causes cirrhosis, liver fibrosis, severe anemia, and enlargement of the liver and spleen, hepatosplenomegaly (Buonfrate et al., 2025). According to Alfred et al. (2025), Egg deposition in the mesenteric circulation results in the detection of *S. mansoni* eggs linked to the mesenteric endothelium of blood vessels and deposited in the liver tissues.

A granulomatous reaction resulting from this causes fibrosis. According to Alfred et al. (2025), granulomatous inflammation-induced fibrosis can result in hepatosplenomegaly, liver portal fibrosis, obstructive vascular lesions, portal hypertension, ascites, and esophagogastric varicose hemorrhage. Both the innate and acquired immune responses contribute to the development of granulomas during *S. mansoni* infection (Takaki et al., 2021). Therefore, the granulomatous environment around the deposited material contains a range of immune cell types, such as eosinophils, macrophages, lymphocytes (B and T cells), dendritic cells, and fibroblasts (Malta et al., 2022). Praziquantel (PZQ) is now the most effective anti-schistosomal medication against adult worms; however, it is less effective against juvenile worms. PZQ was effective in treating schistosomiasis; however, after receiving repeated treatments, worms became resistant to the drug (Nogueira et al., 2022). Furthermore, no effective vaccination against schistosomiasis has been found yet, and research into this topic is still ongoing (Siddiqui et al., 2023). Finding new anti-schistosomal medications to replace PZQ is therefore essential to overcoming its drawbacks (Banda et al., 2025). Anti-schistosomicidal medicinal herbs are thought to be a novel therapy option for schistosomiasis (Azevedo et al., 2023). Curcumin, for example, has strong anti-schistosomal properties and is derived from *Curcuma longa* (Abu Almaaty et al., 2021). The musculature of adult worms is significantly impacted by myrrh, which is derived from *Commiphora molmol*. (Abaza, 2024). Date *Phoenix dactylifera* is one of the most important fruits in many countries all over the world (Al-Karmadi et al., 2024). *P. dactylifera* L. belongs to the Arecaceae family. There are more than 200 genera and 3000 species known worldwide (Albishi et al.,

2025). The fruit of *P. dactylifera* is one of the ancient crops that have been grown in the desert regions of North Africa and the Middle East for thousands of years. *P. dactylifera*'s economic and nutritional significance has led to its expansion into other nations with favorable environmental conditions.

The date palm, *P. dactylifera*, has been a significant part of both human and animal daily life since ancient times (Ibrahim et al., 2024). *P. dactylifera* fruits, seeds, and pollen grains contain high percentages of proteins, vitamins, fibers, carbohydrates, phenolics, and flavonoid compounds that are believed to be potential sources of antioxidants, offering health benefits to humans and other living organisms (Moslemi et al., 2020). Reactive oxygen species (ROS) damage was decreased because of these chemicals' possible actions, which may account for *P. dactylifera's* potential as a therapeutic and protective agent (Al-Shwyeh, 2019). Extracts from *P. dactylifera* may help prevent several chronic illnesses, including diabetes, atherosclerosis, cancer, inflammation, and aging (Moslemi et al., 2020). *P. dactylifera* seeds are by-products of waste that are approximately 10-15% of the weight of dates, which are used for animal feed and in the making of non-caffeinated coffee (Kiesler et al., 2024).

P. dactylifera seeds have potential bioactive materials, for instance, phenolic, flavonoid, and fiber (Nwachukwu et al., 2025). P. dactylifera seeds have been used in traditional medicine for the management of chronic diseases such as diabetes and liver diseases (Almasri et al., 2025). Mineral content in *P. dactylifera* seeds is high (Ibourki et al., 2021). *P. dactylifera* seeds are rich in phenolic and flavonoid chemicals, according to Ghafoor et al. (2015). *P. dactylifera* seeds' antiparasitic effectiveness, especially as an antischistosomal agent, has not been well documented in research. Thus, the purpose of this study was to assess PDSE's potential as an anti-fibrotic and schistosomal agent in mice that had been experimentally infected with *S. mansoni*.

Materials and methods

Chemicals

For the oral treatment of infected mice with *S. mansoni,* praziquantel (PZQ) (Merck KGaA, Darmstadt, Germany) was weighed at quantities sufficient for 500 mg/kg of animal body weight into suitable graduated and labeled containers. Kits for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were obtained from the Bio Diagnostic Company in Egypt. Interleukin 10 (IL-10) and interferon-gamma (INF-gamma) were purchased from Mouse ELISA Kits.

Phoenix dactylifera seeds and extract preparation

Phoenix dactylifera was purchased from a local market in Shobra Elnamla in Tanta City, Egypt. The plant materials were identified and authenticated by a taxonomist at the Botany Department, Faculty of Science, Tanta University. *Phoenix dactylifera* seeds were dried in the shade, then crushed in a mortar, and the powder was kept in a suitable place for further studies. 50 g of seed powder was mixed vigorously with 500 mL of 70% (V/V) ethanol. The hydro-alcoholic extracts were filtered, and the solvent was dried under air conditioning (El-Naggar et al., 2021). Then the extracts were weighed and suspended in 0.9% sterile saline for further processing.

Experimental animals

Fifty albino CD1 male mice weighing 20 ± 3 g were acquired from the Theodor Bilharz Research Institute (TBRI) located in Giza, Egypt. After being moved into an animal facility in Tanta University's Faculty of Science's Zoology Department, mice were given a week to acclimate before trials began. Mice were kept in a 12-hour light/dark cycle with regulated humidity and temperature, and they were allowed unrestricted access to food and drink. The Tanta University Faculty of Science's Experimental Animal Ethical Committee on the Care and Use of Laboratory Animals (IACUC-Sci-TU-0450) gave its approval for the use and care of the animals.

Schistosoma mansoni parasite

The Schistosome Biological Supply Centre (SBSC) at TBRI in Giza, Egypt, provided the infected *Biomphalaria alexandrina* snails. These snails were sent to the Zoology Department's central lab at Tanta University's Faculty of Science. Under artificial light, *S. mansoni* cercaria was shed from snails. Lugol's iodine was used to count the cercaria per milliliter, and the number of cercaria was adjusted to be between 60 and 80.

Experimental plan and treatment protocol

The first group (Gp1) was used as the untreated and uninfected group (n=10) in the laboratory. Forty male mice were infected with 60–80 *S. mansoni* cercariae using the tail immersion technique (Peters and Warren, 1969). Mice infected with *S. mansoni* were split into four groups (n = 10) after four weeks. The infected (positive control) had been Gp2. PZQ (500 mg/Kg) was given orally to Gp3-infected mice for two days in a row. For 15 days in a row, Gp4 received 150 mg/kg of PDSE (Warsinah et al., 2021),

but Gp5 received PZQ/PDSE, the same as Gp3 and Gp4.

Worm burden recovery

By Smithers and Terry (1965), *S. mansoni* worms were recovered by portal perfusion using 0.9% physiological saline. A dissecting microscope was used to count the worms after they had been thrice cleaned with saline. Melman et al. (2009) determined the percentage (%) of worm reduction as follows: % reduction = (C-T/C) X100, where T is the number of adult worms in the treatment group and C is the number of adult worms in the control group.

Egg count determination

As previously reported by Pellegrino et al. (1962), small portions of the liver and ileum tissues of mice infected with *S. mansoni* were weighed and compressed between two slides. Low-magnification microscopy was used to examine the slides. The liver and intestinal tissues' total egg number per gram was determined.

Determination of biochemical parameters

ALT and AST were calculated using Reitman and Frankel's (1957) methodology. We used the Tietze et al. (1994) method to measure serum bilirubin. IL-10 and INF-gamma were found in all experimental groups' serum samples in accordance with the manufacturing criteria.

Histopathology and granuloma measurements

Fixation with 10% formalin was used to fix small sections of the treated groups' liver tissue for a whole night at 4°C. Following histological processing using an escalating alcohol series, the fixed tissues were embedded in paraffin and sectioned at a thickness of 4 µm. Hematoxylin and eosin (H&E) or Masson's trichrome were used to stain the tissue sections. Light microscopy was used to determine the amount of granuloma and hepatic fibrosis (Olympus, Japan). Lesions with a central egg in the liver, stained with H&E, were found using an ocular micrometer to quantify their diameter. After measuring 25 lesions per mouse, the following formula was used to determine the decrease percentage (%R) of granuloma size (GS): % R is equal to the GS of infected mice minus the GS of treated mice divided by 100.

Statistical analysis

All information is presented as mean ± standard deviation (SD) and is based on the means of three replicates. The Kolmogorov-Smirnov test was used to determine normalcy. The impact of metformin on *S. mansoni* burden, hepatic indices, biochemical parameters, and egg count was examined using a two-way ANOVA. To determine significance, Tukey's post hoc comparisons were used. P-values < 0.05 were statistically significant.

Results

Bioactive compounds in *Phoenix dactylifera* seed extract

As shown in Fig. 1, *Phoenix dactylifera* seeds extract presents different chemical constituents at different retention times. The GC-MS analysis of *Phoenix dactylifera* seed extract revealed a diverse profile of bioactive compounds with potential antiparasitic activity. Among the identified constituents were oleic acid, which represented the major component (39.94% and 4.94%); hexadecanoic acid (palmitic acid, detected at 7.18%); hexadecadienoic acid methyl ester (5.64%); and 1,25-dihydroxyvitamin D3 (0.60%) (Table 1).

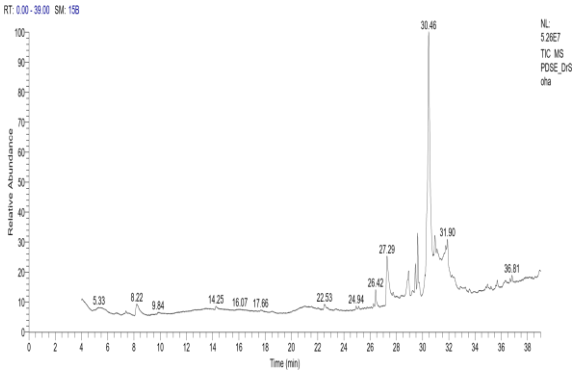


Figure 1. GC-MS chromatogram of *Phoenix dactylifera* seed extract showing the identified compounds at different retention times.

General Composition and Biological Roles

The GC-MS profile of *Phoenix dactylifera* seed extract reveals a complex matrix rich in fatty acids (oleic, palmitic, and linoleic), esters, phenolics, and flavonoid-like compounds. This bioactive works synergistically by disrupting parasite membranes, reducing oxidative stress in host tissues, and modulating immune responses. And enhancing bioavailability through esterification (Table 2)

Treatment with PDSE significantly decreased the total worm burden in *S. mansoni*-infected mice .

S. mansoni-infected mice exhibited a high mean worm burden (14.33 ± 1.21). Treatment with PDSE alone resulted in a moderate worm burden, yet a significant reduction (34.89%). In contrast, the infected *S. mansoni* mice that were treated with PZQ alone or in combination with PDSE showed complete elimination of adult worms (100% reduction) (Table 3).

Table 1. Chemical constituents detected in *Phoenix dactylifera* seeds extracted using GC-MS analysis.

RT	compound name	MF	M.WT	Area %	Library
5.32	3-o-hexopyranosylhex-2-ul ofuranosyl hexopyranoside	C18H32O16	504	0.50	WileyRegistry8e
5.49	d-fructose, diethyl mercaptal, pentaacetate	C20H32O10S2	496	0.55	WileyRegistry8e
5.60	3-o-hexopyranosylhex-2-ul ofuranosyl hexopyranoside	C18H32O16	504	0.49	WileyRegistry8e
7.39	3-oxo-20-methyl-11-à-hydro xyconanine-1,4-diene	C22H31NO2	341	0.44	WileyRegistry8e
8.22	2,3-dihydro-3,5-dihydroxy-6 -methyl-4h-pyran-4-one	C6H8O4	144	2.58	WileyRegistry8e
20.98	2,3-bis-o-(trimethylsilyl)-, cyclic methylboronate	C13H26BNO6Si	331	0.60	mainlib
21.07	à-d-mannopyranoside, methyl, cyclic 2,3:4,6-bis(methylboronate)	C9H16B2O6	242	0.33	WileyRegistry8e
21.53	2,3-bis-o-(trimethylsilyl)-, cyclic methylboronate	C14H31BO6Si2	362	0.36	WileyRegistry8e
22.52	à-d-glucopyranoside, methyl 2-(acetylamino)-2-deoxy-3-o-(trimet hylsilyl)-, cyclic methylboronate	C13H26BNO6Si	331	0.66	WileyRegistry8e
26.42	11,13-dihydroxy-tetradec-5-ynoic acid, methyl ester	C15H26O4	270	1.25	mainlib
27.28	hexadecanoic acid	C16H32O2	256	7.18	WileyRegistry8e
27.74	2-bromotetradecanoic acid	C14H27BrO2	306	0.54	mainlib
28.93	à-d-galactopyranose, 6-o-(trimethylsilyl)-,cyclic 1,2:3,4-bis(butylboronate)	C17H34B2O6Si	384	3.05	WileyRegistry8e
29.26	androstan-17-one, 3-ethyl-3-hydroxy-, (5à)	C21H34O2	318	0.55	mainlib
29.45	9,12-octadecadienoic acid, methyl ester	C19H34O2	294	2.02	mainlib
29.62	10-octadecenoic acid, methyl ester	C19H36O2	296	3.35	mainlib
29.74	2-hydroxy-3-[(9e)-9-octadec enoyloxy]propyl (9e)-9-octadecenoate	C39H72O5	620	0.89	WileyRegistry8e
30.18	methyl-9,9,10,10-d4-octadeca noate	C19H34D4O2	302	0.93	WileyRegistry8e
30.46	oleic acid	C18H34O2	282	39.94	mainlib
30.83	(9e,12e)-9,12-octadecadieno yl chloride	C18H31ClO	298	1.55	WileyRegistry8e
30.93	oleic acid	C18H34O2	282	4.94	replib
31.09	hexadecadienoic acid, methyl ester	C17H30O2	266	5.64	WileyRegistry8e
31.36	9,12-octadecadienoic acid (z,z)-, trimethylsilyl ester	C21H40O2Si	352	2.08	WileyRegistry8e
31.54	linolsaeure, trimethylsilylester	C21H40O2Si	352	1.71	WileyRegistry8e
31.62	9,12-octadecadienoic acid (z,z)-, tms derivative	C21H40O2Si	352	1.46	WileyRegistry8e
31.67	linoelaidic acid, trimethylsilyl ester	C21H40O2Si	352	0.79	replib
31.76	trimethylsilyl (6e)-6-octadecenoate	C21H42O2Si	354	2.39	WileyRegistry8e
31.90	11-cis-octadecenoic acid 1tms	C21H42O2Si	354	4.15	WileyRegistry8e
32.43	á-d-glucopyranoside, methyl 2,3-bis-o trimethylsilyl)-, cyclic methylboronate	C14H31BO6Si2	362	0.60	WileyRegistry8e
32.88	hexadecadienoic acid, methyl ester	C17H30O2	266	0.40	WileyRegistry8e
33.26	6,9,12,15-docosatetraenoic acid, methyl ester	C23H38O2	346	0.37	mainlib
34.82	6,9,12,15-docosatetraenoic acid, methyl ester	C23H38O2	346	0.32	mainlib
34.94	dasycarpidan-1-methanol, acetate (ester)	C20H26N2O2	326	0.54	mainlib
35.69	linoleic acid ethyl ester	C20H36O2	308	0.66	replib
36.33	1,25-dihydroxyvitamin d3, tms derivative	C30H52O3Si	488	0.60	mainlib
36.67	4h-1-benzopyran-4-one, 2-(3,4-dimethoxyphenyl)-3,5dihydroxy-7-methoxy	C18H16O7	344	0.42	WileyRegistry8e
36.80	ethyl iso-allocholate	C26H44O5	436	0.57	mainlib
38.91	tricyclo[20.8.0.0(7,16)]triacontane, 1(22),7(16)-diepoxy	C30H52O2	444	0.42	mainlib
39.82	linoleic acid ethyl ester	C20H36O2	308	0.41	replib

PDSE treatment reduced the ova deposition in S. mansoni-infected mice

Tissue egg load was also markedly decreased in PDSE-treated animals, with a mean count of 513.83 ± 114.32 ova/mouse, corresponding to an 86.97% reduction compared to *S. mansoni*-infected mice alone, where the mean ova count was 3948.8 ± 598.29 ova/mouse. No eggs were detected in the PZQ or PZQ+PDSE groups (Figure 2). Oogram analysis revealed that the untreated *S. mansoni* infected group had 50.17% immature, 44.83% mature, and only 5% dead ova. PDSE-treated *S. mansoni* mice exhibited 30.33% immature, 46.83% mature, and 22.83% dead ova, indicating interference with egg viability (Figure 3). Treatment of *S. mansoni*-infected mice with PZQ/PDSE resulted in complete ovicidal activity (100% dead ova).

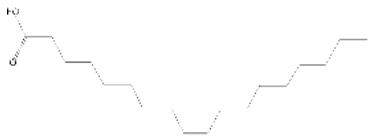
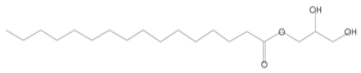
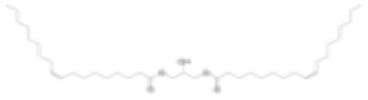
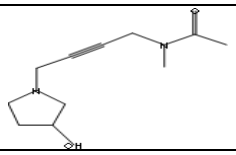
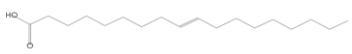
Treatment with PDSE decreased IL-10 and INF-γ levels and improved the liver function in S. mansoni-infected mice.

Serum analysis demonstrated elevated levels of inflammatory cytokines and hepatic enzymes in the infected control group, including IL-10 (~216–296 pg/ml), INF-γ (~206–296 pg/ml) (Figure 4), ALT (97–101 IU), AST (89–94 IU) (Figure 5), and serum bilirubin (1.1–1.2 mg/ml) (Figure 6). Treatment with PDSE significantly ameliorated these parameters. Notably, IL-10 and INF-γ were reduced to ~187–189 pg/ml and ~192–194 pg/ml, respectively, as shown in Figure 4, while liver enzyme levels declined to within moderately elevated ranges.

PZQ treatment led to further improvements, with ALT and AST dropping to 36–40 IU and 31–33 IU, respectively (Figure 5). The combination of PZQ and PDSE yielded near-normalization of all parameters, with INF-γ levels around 32–38 pg/ml and ALT and AST levels at 31–38 IU and 28–30 IU, respectively (Figures 4 and 5).

Quantitative granuloma analysis showed a significant reduction in granuloma diameter and a shift in composition across treatment groups (Table 4). Infected controls had granulomas ranging from 250 to 350 µm, with 75% of these being fibro cellular. PDSE treatment reduced granuloma size to 210–310 µm and fibro-cellular composition to 60%. The PZQ+PDSE group displayed granulomas of 190–320 µm with 95% fibro-cellular or worm granulomas, indicating a transition toward healing. Inflammatory cell profiles shifted from neutrophil dominance in infected controls to predominance of eosinophils and macrophages in treated groups (Table 4).

Table 2. Key Bioactive Compounds and Their Antiparasitic Potential

Compound	Area %	Biological Interpretation	Compound Structure
Oleic acid	39.94% + 4.94%	Monounsaturated fatty acid with antiparasitic and anti-inflammatory effects. Disrupts parasite membranes.	
Hexadecanoic acid (Palmitic acid)	7.18%	Saturated fatty acid with antimicrobial and antiparasitic activity via membrane disruption.	
9,12-Octadecadienoic acid (Linoleic acid) and derivatives	~9%	Polyunsaturated fatty acids known for immune modulation and inducing apoptosis in parasites.	
Hexadecadienoic acid, methyl ester	5.64%	Fatty acid ester with antimicrobial potential contributing to antiparasitic effects.	
2-hydroxy-3-[(9E)-9-octadecenoyloxy]propyl (9E)-9-octadecenoate	%3.35	antiparasitic properties, particularly against protozoan parasites such as *Acanthamoeba spp.*	

Compound	Area %	Biological Interpretation	Compound Structure
1,25-Dihydroxyvitamin D3, TMS derivative	0.60%	Vitamin D3 analogue enhances innate immunity and regulates inflammation.	
Linoleic acid ethyl ester	+%551. +%0.89 +%0.66 +%0.42 +%0.41 +%0.42 0.32	Ester with reported antiparasitic effects against cestodes in animal models.	

Table 3. The worm burden in the liver and Porto-mesenteric and total worm burden reduction in different groups

Experimental groups	**Mean worm burden ± SD (liver and Porto-mesenteric)**				**% total worm burden reduction**
	Male	**Female**	**Couples**	**total**	
S. mansoni-infected mice	3±0.63	0	5.67±0.52	14.33±1.2	
S. mansoni-infected mice / PZQ	0	0	0	0	100
S. mansoni-infected mice/PDSE	3.5±0.5	0.17±0.4	2.83±0.75	9.33±1.21	34.89
S. mansoni-infected mice / PZQ/PDSE	0	0	0	0	100

PZQ: Praziquantel; PDSE: *P. dactylifera* seeds extract

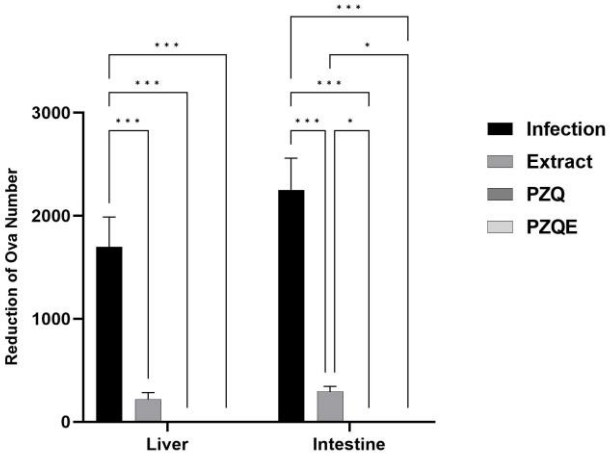


Figure 2. The number of ova deposited in *S. mansoni-infected* mice treated with PDSE and groups treated with PZQ alone or in combination with PDSE in both the intestine and liver tissue, compared to the infected-untreated control group.

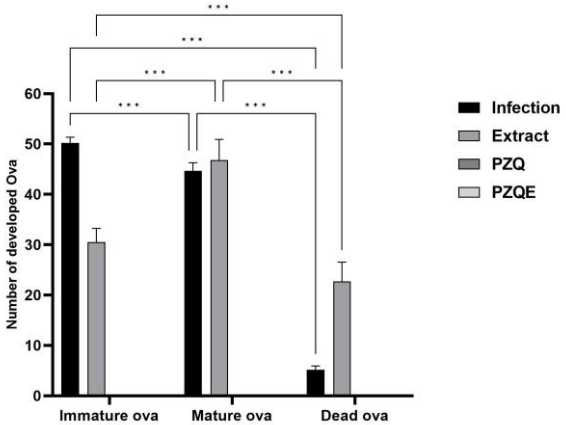


Figure 3. The degenerated ova number in *S. mansoni-infected* mice treated with PDSE and groups treated with PZQ alone or in combination with PDSE compared to the infected-untreated control group**.**

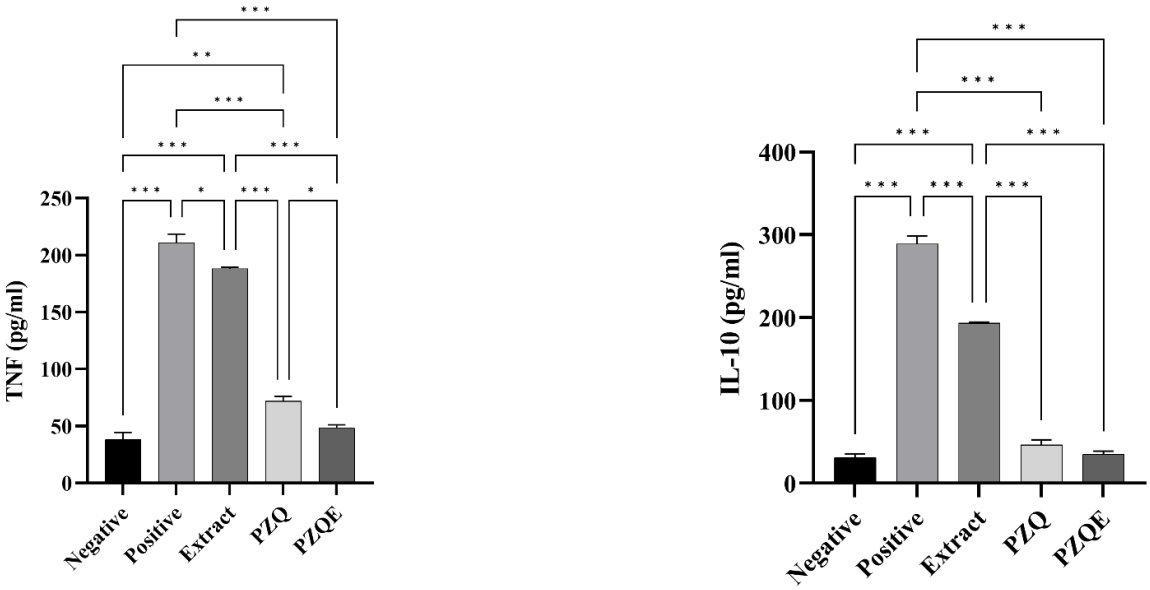


Figure 4. TNF and IL-10 in *S. mansoni*-infected mice as well as in groups treated with PZQ alone or in combination with PDSE compared to the infected-untreated control group**.**

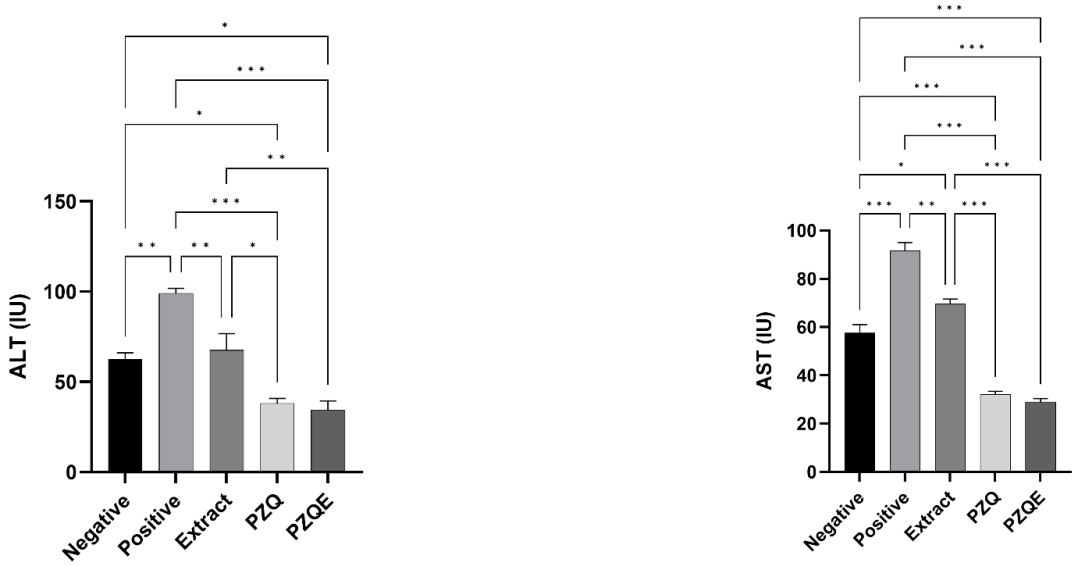


Figure 5. Liver enzymes ALT and AST in PDSE treatment in the *S. mansoni* infected group**,** while PZQ alone or a combination of PZQ and PDSE compared to the infected-untreated control group.

Histological sections of infected liver tissue displayed extensive fibro-cellular granulomas with central ova, intense portal inflammation, and frequent Schistosoma worms obstructing the portal veins (Figure 7). PZQ-treated liver sections showed the absence of granulomas, with focal portal and lobular inflammatory infiltrates. PDSE-treated sections revealed cellular and fibro-cellular granulomas with reduced inflammatory infiltration and occasional degenerated worms (Figure 8). Notably, livers from the PZQ+PDSE group showed minimal granulomatous inflammation, presence of worm granulomas, mild portal fibrosis, and signs of tissue remodeling (Figures 7, 8). In histological results, PDSE shows partial anti-fibrotic activity, attenuating granuloma size and inflammation.

Discussion

This study demonstrated that an extract from *Phoenix dactylifera* seeds has an anti-schistosomal effect on mice infected with *Schistosoma mansoni*. Hepatic fibrosis, a serious pathological alteration that leads to a loss of liver function, is brought on by an *S. mansoni* infection and manifests as an inflammatory reaction with variable degrees of cirrhosis (Müller et al., 2024). PZQ, the primary chemotherapeutic treatment option for *S. mansoni*, is effective only on mature worms and has no anti-fibrotic impact (Membe Femoe et al., 2022).

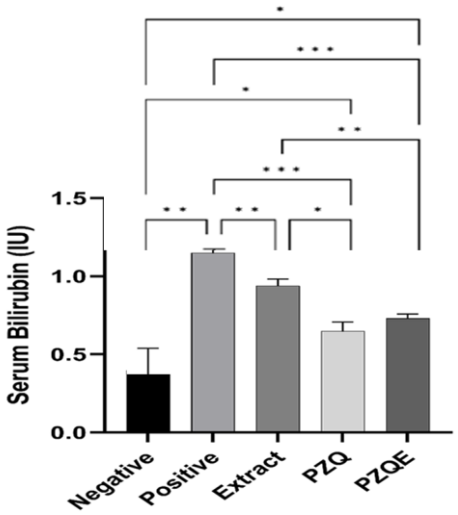


Figure 6. Serum bilirubin levels in PDSE treatment in *the S. mansoni* infected group**,** as well as in both PZQ and a combination of PZQ and PDSE treated groups, compared with the infected-untreated control group.

There is still a need for new, potent anti-schistosomal medications to replace PZQ. It was discovered that several medications, including PZQ, reduced the number of eggs and worm load in tissue without reducing fibrosis (Salama et al., 2021). Thus, the idea of adding anti-fibrotic therapies as adjuvants to the anti-schistosomal chemotherapy, either by themselves or in conjunction with the conventional anti-schistosomal medications, may aid in the treatment of the infection. The total number of eggs in the liver and intestinal tissues of S. mansoni-infected mice was significantly reduced because of PZQ treatment, according to the data. This result was in line with another study that found that PZQ treatment significantly decreased the viability of eggs in liver tissue (Salama et al., 2021).

Certain medicinal plants include natural chemicals that have strong anticancer and antioxidant properties, and they may also lessen the negative effects of chemotherapy (El-Naggar et al., 2018). In a mouse model of S. mansoni infection, the current work demonstrates the noteworthy anti-schistosomal, ovicidal, anti-inflammatory, and anti-fibrotic actions of PDSE. Alone, GC-MS analysis of Phoenix dactylifera seed extract revealed a rich spectrum of bioactive compounds, notably fatty acids, esters, phenolics, and flavonoid-like molecules, many of which are well-documented for their antiparasitic and immunomodulatory properties. Among these, oleic acid was the most abundant, constituting nearly 45% of the extract. This monounsaturated fatty acid has been shown to disrupt parasite membranes and inhibit their viability through cytotoxic and anti-inflammatory mechanisms (El-Sheekh et al., 2019; Ibrahim et al., 2024). In addition, palmitic acid (hexadecanoic acid), a saturated fatty acid, was identified at a substantial percentage (7.18%). It is known to exert antimicrobial and antiparasitic effects via disruption of lipid bilayers and induction of oxidative stress (Nasir et al., 2015). Linoleic acid and its esters, representing ~9% of the composition, play a significant role in immunological signaling and may promote apoptosis in parasites through lipid peroxidation and membrane destabilization (El-Naggar et al., 2018; Abaza, 2024).

The detection of hexadecadienoic acid methyl ester further supports the extract's potential, as esters are known to enhance compound stability and cellular uptake, thereby increasing antiparasitic efficacy (Moslemi et al., 2022). The presence of 1,25-dihydroxyvitamin D3 suggests that the extract may support innate immune responses and modulate inflammatory pathways (Ibourki et al., 2021). Furthermore, the extract contains a significant diacylglycerol compound, 2-hydroxy-3-[(9E)-9-octadecenoyloxy]propyl (9E)-9-octadecenoate (also known as DG (18:1/0:0/18:1)). This compound has demonstrated notable antimicrobial and antiparasitic properties, particularly against These compounds have been shown to disrupt parasite metabolism, inhibit egg maturation, and induce oxidative stress in helminths (Nasir et al., 2015).

The increase in dead ova and reduction in immature forms in the oogram analysis support the hypothesis that PDSE interferes with egg development and viability. PDSE also demonstrated a notable capacity to modulate immune responses, as evidenced by significant reductions in pro-inflammatory cytokines (IL-10, INF-γ) and normalization of liver enzymes (ALT, AST). According to these results, the antioxidant activity of polyphenols and flavonoids', which scavenge reactive oxygen species and inhibit inflammatory mediators, may have an anti-inflammatory effect (Al-Shwyeh, 2019; Mia et al., 2020). This process is in line with other research showing the immunomodulatory and hepatoprotective benefits of natural extracts in inflammatory and parasitic illnesses (El-Naggar et al., 2018).

According to histopathological analysis, PDSE reduces hepatic granulomatous inflammation. Perhaps because of inhibiting fibroblast activation and collagen deposition, the observed decrease in granuloma size and inflammatory cell infiltration is consistent with its anti-fibrotic qualities. The PDSE and PZQ/PDSE groups had smaller, less cellular granulomas, and the composition of granulomas changed from fibro-cellular to worm and resolved granulomas, which supports this. These alterations are suggestive of successful tissue remodeling and parasite removal (Hassanpour et al., 2023).

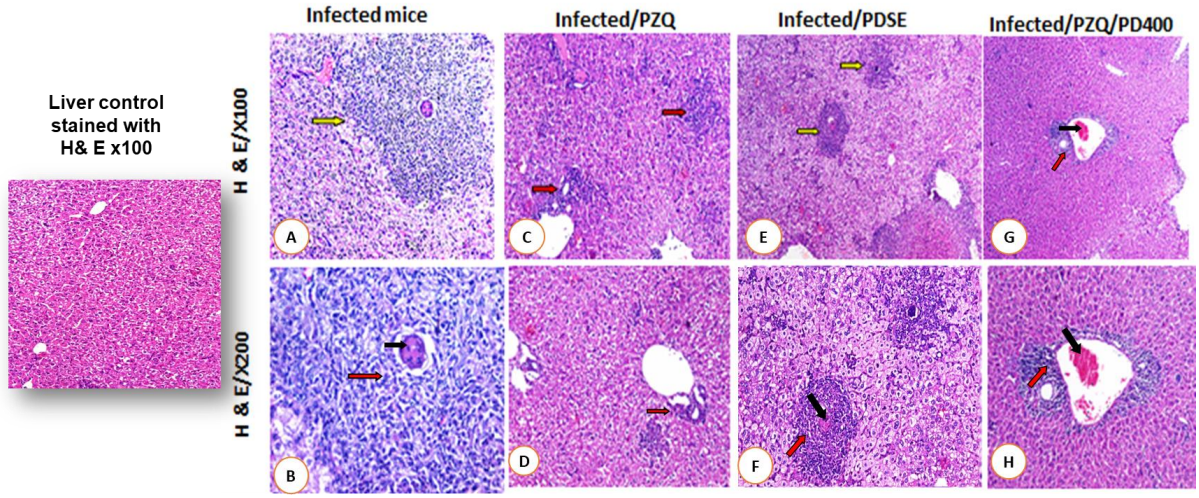


Figure 7. A-H (H & E stain): Photograph of sections in the liver of the infected control group showing fibro-cellular egg granuloma (yellow arrow) with central ova (black arrow) and fibro-cellular component (red arrow) (A-B). The section in the liver tissue of infected-PZQ-treated mice shows the absence of egg granulomas and focal portal and lobular infiltration by inflammatory cells (red arrows) (C-D). Sections in the liver of extract-treated mice showing some cellular egg granulomas (yellow arrows) with central ova (black arrow) surrounded by inflammatory cells (red arrows) (E-F). Sections in the liver of Extract + PZQ-treated mice showing an ovum inside a portal vein (black arrow) and mild portal inflammatory cellular reaction (red arrow) (G-H).

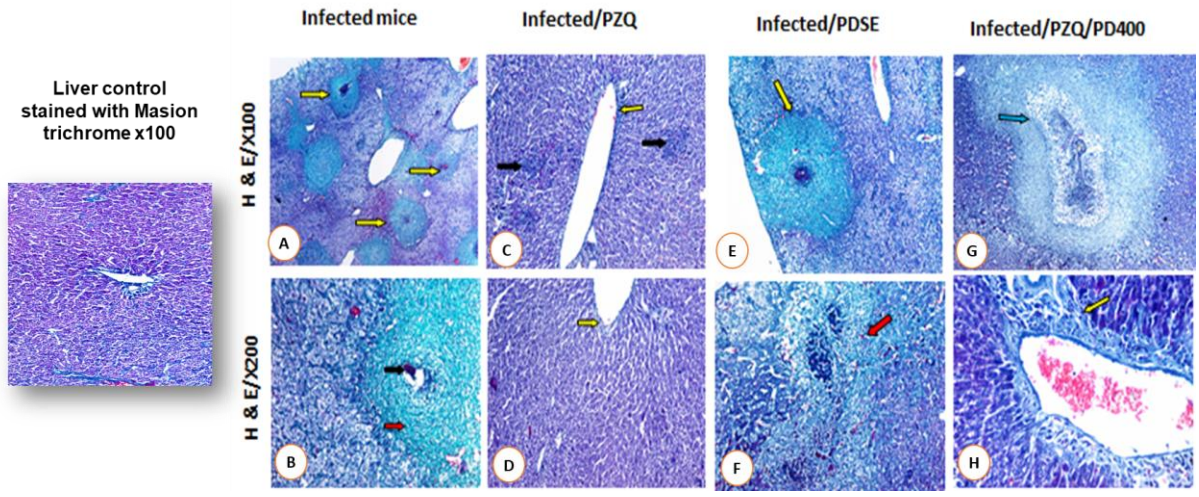


Figure 8. A-H (Masson's trichrome stain): Photograph of sections in the liver of the infected control group showing multiple egg granuloma (yellow arrows) with central ova (black arrow) and fibro-cellular component (red arrow) (A-B). The section in the liver tissue of infected-PZQ-treated mice showed mild portal tract fibrosis (yellow arrows) and a few small fibrous granulomas (black arrows) (C-D). Sections in the liver of extract-treated mice showing fibro-cellular egg granulomas (yellow arrows) with an inflammatory reaction around the degenerated worm (red arrow) (E-F). Sections in the liver of Extract +PZQ-treated mice showing a fibro-cellular worm granuloma, round degenerated worm (blue arrows), and mild portal fibrosis (yellow arrow) (G-H).

Taken together, the findings indicate that PDSE exerts a multifaceted protective effect in schistosomiasis: it contributes to parasitic control, reduces egg-induced pathology, and supports tissue healing through modulation of host immune responses. When used in combination with PZQ, these effects are amplified, suggesting a synergistic interaction. This is consistent with the more general therapeutic justification for combining anti-inflammatory and antiparasitic drugs to get around the drawbacks of monotherapy and stop the progression of the disease (Keiser and Utzinger, 2010). Study Limitations: This study has several limitations that should be acknowledged. Firstly, only one type of *Phoenix dactylifera* seed extract was used, without comparing the effects of different extraction methods or parts of the plant (e.g., pulp, leaves, or whole fruit), which may have different phytochemical profiles and therapeutic potentials. Secondly, the active compounds responsible for the

Table 4. Granuloma diameter, composition, and inflammatory cell profiles in experimental groups.

Group	Schistosoma egg-granuloma						
	count	**diameter**	**c**	**Fc**	**f**	**OVA**	**Cells**
–ve control	-	-	-	-	-	-	-
+ve control	6, 5, 5, 7, 8, 7, 13, 15, 10, 14	350, 320, 250, 350, 190, 280, 320	25%	75%	-	Intact +++ Deg. +	N ++ L ++ M- E+ P+
PZQ	3, 2, 2, 2, 3, 4	250, 190, 200, 150, 230, 180	5%	95% + W G	-	Intact + Deg. +++	N ++ L ++ M++ E+ P++
EXT	5, 6, 5, 3, 4, 5	310, 250, 230, 210, 270, 300	40%	60%	-	Intact +++ Deg. +	N ++ L + M- E++ P+
PZQ+EXT	4, 2, 4, 3, 3 ,4	320, 270, 220, 230, 320, 190	5%	95% +++ W G	-	Intact + Deg. +++	N + L ++ M++ E+ P++

Count: in 5 successive 100X fields.

Diameter: in microns

c: cellular egg granuloma

Fc: fibro-cellular egg granuloma

f: fibrous egg granuloma

WG: worm granuloma

N: neutrophils L: lymphocytes M: macrophages E: eosinophils P: Plasma cells

observed anti-schistosomal effects were not isolated or identified, limiting our understanding of the specific bioactive constituents involved. Thirdly, although in vivo assessments were conducted, no in vitro experiments were performed to evaluate the extract's direct effect on different developmental stages of *Schistosoma mansoni*, particularly the larval stages, which could provide more mechanistic insights. Addressing these limitations in future studies will enhance the scientific robustness and translational potential of the findings.

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Conflict of interest

The authors declare that there is no conflict of interest.

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