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Original article

Evaluation of nanoselenium and nanogold activities against murine intestinal schistosomiasis

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ABSTRACT

Nanomedicine is one of the most important methods used to treat human diseases including parasitic diseases. Schistosomiasis is a major parasitic disease that affects human health in tropical regions. Whilst Praziquantel is the main classic antischistosomal drug, new drugs are required due to the poor effect of the drug on the parasite juveniles and immature worms, and the emergence of drug resistant strains of *Schistosoma*. The present study aimed to examine the curative roles of both gold and selenium nanoparticles on jejunal tissues of mice infected with *Schistosoma mansoni*. Transmission electron microscopy was used for characterization of nanoparticles. Gold nanoparticles of 1 mg/kg mice body weight and selenium nanoparticles 0.5 mg/kg body weight were inoculated separately into mice infected with *S. mansoni*. The parasite induced a significant decrease in glutathione levels; however, the levels of nitric oxide and malondialdehyde were significantly increased. Additionally, the parasite introduced deteriorations in histological architecture of the jejunal tissue. Treatment of mice with metal nanoparticles reduced the levels of body weight changes, oxidative stress and histological impairment in the jejunal tissue significantly. Therefore, our results revealed the protective role of both selenium and gold nanoparticles against jejunal injury in mice infected with *S. mansoni*.

1. Introduction

Nanomedicine is a nanotechnology application for treatment, monitoring, prevention, and control of biological diseases (Abaza, 2016). Nanoparticles (NPs) of some metals or metal oxides are now widely used as drugs to treat different diseases and improve human health due to their antimicrobial actions; these NPs with specific chemical and physical features have shown anti-bacterial, antiviral and anti-parasitic actions against these pathogens (Tran and Webster, 2011; Jebali and Kazemi, 2013).

Selenium, gold and silver NPs and oxide NPs of titanium, zinc and magnesium have demonstrated antileishmanial activities (Jebali and Kazemi, 2013; Jamshidi et al., 2014). Antischistosomal role of selenium nanoparticles (SeNPs) against hepatic injury in mice was demonstrated by Dkhil et al. (2016a), additionally, the team has presented the antischistosomal activity of gold nanoparticles (GNPs) in different tissues of mice e.g. liver, brain, kidney and spleen respectively (Dkhil et al., 2015a,b, 2016b, 2017).

Schistosomiasis, an acute and chronic parasitic disease caused by blood flukes of the genus *Schistosoma*, is still counted as one of the dangerous diseases that mostly affects poor people in tropical and subtropical regions of the world, particularly those in rural areas, and who depend on agriculture and fishing (Hotez, 2006). In 2015, more than 61.6 million people have been treated for schistosomiasis. However, it was also estimated that more than 258

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million people still need the treatment (WHO, 2015), and more than 800 million people are susceptible to infection in tropical regions of Africa, the Middle East, and Central and South America (Steinmann et al., 2006).

It is well-known that the pathogenic effects of the parasite on the mammalian definitive hosts is not principally related to the adult worms (Gryseels et al., 2006), but results from the chronic inflammatory granulomatous reactions in response to the massive egg production by the parasite in the liver and other tissues such as intestine, spleen, bladder, and lungs (Araújo et al., 2010; Wang et al., 2015; Dkhil et al., 2017). Intestinal schistosomiasis caused by *Schistosoma mansoni* is the most widespread disease caused by this parasite in Africa, the Middle East, the Caribbean, Brazil, Venezuela, and Suriname (WHO, 2015).

Intestinal and/or urinary system bleeding and hepatosplenomegaly are the major pathological symptoms of chronic schistosomiasis (Burke et al., 2009). It was found that mice chronically infected with *S. mansoni* suffer from intestinal inflammation and granulomatous reactions in the mucosa and submucosa (Bauomy et al., 2014), and enlargement of both the liver (Chen et al., 1993) and spleen (Chen et al., 1993; Dkhil et al., 2017). The intestine represents the major organ of food digestion and nutrient absorption, in addition to its immune role; therefore, migration of schistosome eggs through its wall induces mucosal inflammation, pseudopolyps, ulceration and bleeding (Cheever et al., 1978).

In endemic areas, treatment of schistosomiasis is still dependent on Praziquantel (PZQ), the classic drug which is safe, low cost and effective against all *Schistosoma* species (WHO, 2015; Hotez et al., 2007). However, it is ineffective against the parasite juveniles "schistosomules" and immature worms, and thus unsuitable for mass treatment in high endemic regions (Doenhoff et al., 2008). The over- use of the drug in endemic areas led to appearance of resistant strains of the parasite PicaMattoccia et al., 2009), also PZQ must be used in higher doses due to its poor absorption in the intestine (Mourão et al., 2005), and patients treated with the drug remain vulnerable to reinfection (Cioli and Pica-Mattoccia, 2003). Therefore, looking for other safe and effective antischistosomal drugs to replace, or be used in association with PZQ, was and still is a necessity. Therefore, the current research is an extension to a series of studies made by Dkhil et al. (2015a,b, 2016a,b, 2017) to address the therapeutic antischistosomal effects of the NPs of both selenium and gold on the jejunum of mice infected with the *S. mansoni*.

2. Materials and methods

2.1. Gold NPs and selenium NPs preparations

Selenium nanoparticles (50–100 nm particle size) were obtained from Nano-tech Lab in 6 October City, Egypt, as a sterilized solution, as they were dispersed in phosphate buffered saline (PBS) and ready for use. In brief, a simple wet chemical method has been developed to synthesize selenium nanoparticles, by the reaction of sodium selenosulphate precursor with deferent organic acids in aqueous medium, under ambient conditions. Polyvinyl alcohol has been used to stabilize the SeNPs. The synthesized nanoparticles can be separated from its sol by using a high-speed centrifuge and can be re-dispersed in aqueous medium with a sonicator (Dwivedi et al., 2011). Transmission electron microscope (TEM) was used for characterization of nanoparticles (shape and size).

Gold NPs have been prepared by chemical reduction method (Turkevich et al., 1951). "HAuCl4" solution has been used as $Au3^{+}$ ions precursor; while sodium citrate has been used as both of mild reducing and stabilizing agent. The color of the solution slowly turned into faint pink color, indicating the reduction of the $Au3^{+}$ ions to GNPs. By transmission electron microscopy (TEM); size and morphology of GNPs were determined. Samples for TEM were prepared using the clear solution of NPs. The sample solution was put on a formvar coated grid. On this grid, a drop of the sample solution (containing dispersed NPs) was placed and allowed to air-dry. A TEM picture was taken by a JOEL JEM 2000 EX200 microscope.

2.2. Scistosomiasis mansoni infection

In the present study; we purchased 42 Swiss albino male mice from Schistosome Biological Supply Center at Theodor Bilharz Research Institute, Imbaba, Giza, Egypt. Mice (9–11) weeks of age were maintained under specified pathogen-free conditions and fed on standard diet. Diet and water were provided ad libitum. Mice infection was carried out by subcutaneous injection of "100 ± 10" *S. mansoni* cercarie (Oliver and Stirewalt, 1952). The experiments were approved by state authorities and followed the scientific rules for animal protection.

2.3. Animal grouping

Mice were divided into 5 groups (6 mice per each group). The first group was served as a non-infected group, where each mouse was intubated (100 μl water/mouse) for 10 days. The remaining 24 mice were infected with "100 ± 10" *S. mansoni* cercarie then divided into 4 groups, 46 days post-infection (p.i.).

Six infected mice were considered as the infected; untreated group (2nd group). The remaining three groups were treated with SeNPs (0.5 mg/kg body weight) for 7 consecutive days (3rd group); GNPs (i.p; 1 mg/kg mice body weight), twice per week on day 46 and day 49 p.i. (4th group) while; the mice of 5th group were orally administered with 600 mg/kg of PZQ on day 46 p.i. at an interval of 24 h for 2 days (Gonnert and Andrews, 1977). The dose of GNPs was chosen according to Dkhil et al. (2015a) while that of SeNPs was chosen according to Hassanin et al. (2013).

2.4. Biochemical parameters

Jejunum was immediately excised and weighted then homogenized immediately to give 50% (w/v) homogenate in ice-cold Tis-HCl buffer (Tsakiris et al., 2004). The homogenate was centrifuged at 500*g* for 10 min. The supernatant (10%) was used for determination of glutathione, nitrite/nitrate and malondialdehyde.

The glutathione (GSH) level in jejunum was determined by the method of Ellman (1959), in addition, the nitrite/nitrate and malondialdehyde (MDA) levels were assayed according to the methods of Green et al. (1982) and Ohkawa et al. (1979), respectively.

2.5. Histopathological investigations

Mice were sacrificed by fast decapitation on day 56 p.i. Jejunum was immediately removed, fixed in 10% formalin, dehydrated, embedded in paraffin, sectioned and stained with haematoxylin and eosin for histopathological studies. Stained sections of jejunum were scored by Dommels et al. (2007) method for incendiary lesions, as shown by infiltrations of mononuclear cells, neutrophils, eosinophils, plasma cells and furthermore for tissue destruction and tissue repair. A rating score between 0 (no change from normal tissue) and 3 (lesions involved most areas and all the layers) was given for each aspect of inflammatory lesion, tissue destruction, and tissue repair. The sum of inflammatory lesions (doubled to give more weight to this parameter), tissue destruction and tissue

repair scores were used to represent the total histological injury score.

2.6. Statistical analysis

The obtained data were presented as means ± standard error. One-way ANOVA was carried out, and the statistical comparisons among the groups were performed with Duncan's test using a statistical package program (SPSS version 17.0). $P < 0.05$ was considered as low, moderate and highly significant for all statistical analysis in this study.

3. Results

The TEM proved the size and shape of both selenium and gold NPs, where the average size of SeNPs was less than100 nm with spherical like shape (Fig. 1A). In addition; GNPs were observed to be spherical in shape, with an average diameter of 20 ± 5 nm using electron microscopy (Fig. 1B).

Fig. 2 cleared that *Schistosomiasis mansoni* induced a significant increase at ($P < 0.05$) in mice body weight as compared to non-infected group. Moreover, treatment of the schistosome infected mice with SeNPs decreased the body weight significantly when compared with the infected group, likewise, injection of GNPs, and PZQ to schistosome infected mice resulted in a significant reduction in body weight versus schistosome infected animals. On the other hand, a non-significant change was observed in mice body weight resulting from treatment with SeNPs, GNPs, PZQ as compared to the non-infected group, and revealing improvement of the animal body weight changes induced by infection.

On the other hand, the infection induced a significant reduction in GSH level in jejunum, on the other hand, a significant increase was found in jejunal nitrite/nitrate and MDA levels as compared to non-infected group. Treatment with NPs of either selenium or gold to schistosome infected mice increased GSH level significantly, meanwhile, PZQ treatment showed a significant increase. Oppositely, treatment with SeNPs, GNPs and PZQ induced a significant decrease in nitrite/nitrate and MDA levels in jejunum as compared to infected group (Table 1).

Histologically, the jejunum of the non-infected mice revealed a well preserved cellular integrity. There was no evidence of cellular degeneration, necrosis, when viewed under a light microscope (Fig. 3). Also, the epithelial lining of the mucosa was intact, and no vacuolations were seen, while the histopathological examination of the jejunum of the infected; non-treated mice showed evidence of chronic inflammation of the jejunum. In SeNPs, GNPS and PZQ treated groups, the jejunum showed apparent amelioration where fewer lesions in the jejunal tissues (Fig. 3). The histological analysis and scoring of the jejunum sections (Fig. 4) showed that mice infected with *Schistosoma mansoni* suffered a severe inflammatory injury when compared to score of non-infected mice and score of treated groups of SeNPs, GNPS and PZQ showed a significant decrease than infected group but still significantly increase when compared with the score of the non-infected mice (Fig. 4).

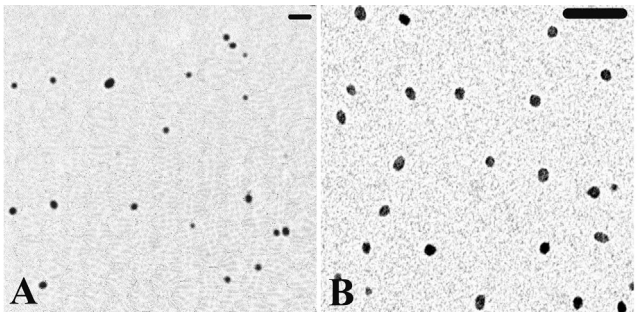

Fig. 1. Transmission electron microscopy image of the SeNPs (A) and GNPs (B) illustrates their shape and size. Scale bar indicates 100 nm.

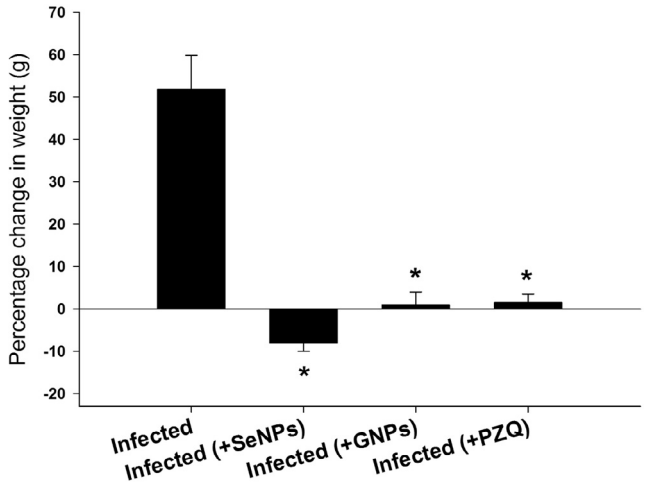

Fig. 2. Effect of SeNPs and GNPs on the body weight of mice infected with *S. mansoni*. Values are means of the percentage change in weight compared to the non-infected mice ± SD. *: Significant against infected group at $P \leq 0.05$.

Table 1
Effect of SeNPs and GNPs on glutathione (GSH), nitrite/nitrate, and malondialdehyde (MDA) levels in jejunal homogenate of mice infected with *S. mansoni*.

Group	GSH (mg/g)	Nitrite/nitrate (μmol/g)	MDA (nmol/g)
Non-infected	71.19 ± 2.94	67.74 ± 1.45	19.03 ± 1.00
Infected	40.80 ± 1.84[a]	240.3 ± 11.4[a]	47.90 ± 2.42[a]
Infected (+SeNPs)	53.58 ± 3.42[ab]	188.4 ± 3.33[abc]	36.27 ± 2.26[abc]
Infected (+GNPs)	55.50 ± 1.81[ab]	156.9 ± 2.55[ab]	26.05 ± 1.61[ab]
Infected (+PZQ)	49.19 ± 1.85 [ab]	203.0 ± 8.18 [ab]	40.98 ± 1.5 [ab]

Values are means ± SE. a: Significant against non-infected group at $P \leq 0.05$, b: Significant against infected group at $P \leq 0.05$, c: Significant against nano-treated group, n = 6.

4. Discussion

Nanoparticles usually have greater efficacy but less damage effects on cells than other forms of their metals (Shakibaie et al., 2010), their specific chemical and physical features, such as having great surface areas allow them to interact with microbiological organisms, and their size permit them to access the cells. They have shown anti-bacterial, antiviral and anti-parasitic actions (Tran and Webster, 2011; Jebali and Kazemi, 2013).

Schistosoma mansoni egg deposition causes chronic inflammatory reactions in intestinal tissue with production of reactive oxygen intermediates with subsequent oxidative stress (Hope et al., 2005). The results of the current study revealed a significant decrease in GSH level and a significant elevation in nitrite/nitrate and MDA levels in mice jejunum as a result of *Schistosomiasis mansoni* infection. Our results are in agreement with Mantawy et al. (2011) and Mahmoud and Elbessoumy (2013).

Mantawy et al. (2011) found that levels of GSH and vitamins (C & E) were significantly decreased, while level of lipid peroxidation was significantly increased after *Schistosoma mansoni* infection. Tielens (1994) reported that the infected host was subjected to oxidative stress or increased free radical formation where

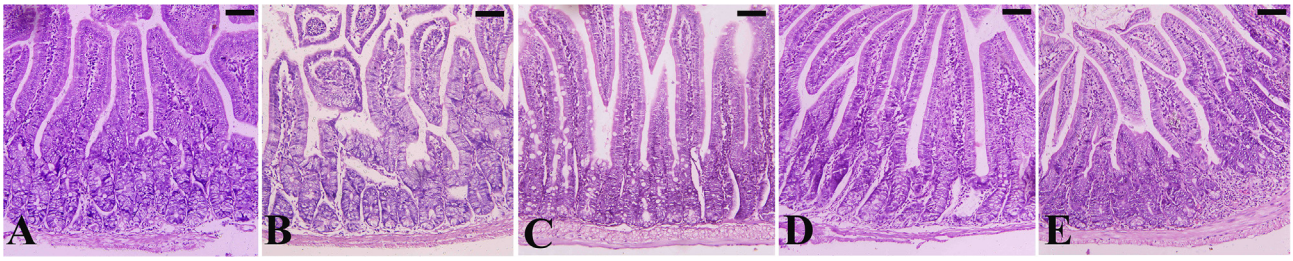

Fig. 3. Histopathological changes in the jejunal tissue of non-infected, infected, and treated mice post infection with *Schistosoma mansoni*. (A) Non-infected jejunum with normal architecture. (B) Infected jejunum with granuloma with large accumulation of inflammatory cells. (C, D and E) Jejunum of infected treated mice with SeNPs, GNPs and PZQ, respectively, sections appeared with improved tissue damage showing fewer lesions and absence of granuloma or smaller granuloma size. Sections are stained with hematoxylin and eosin. Bar = 100 μm.

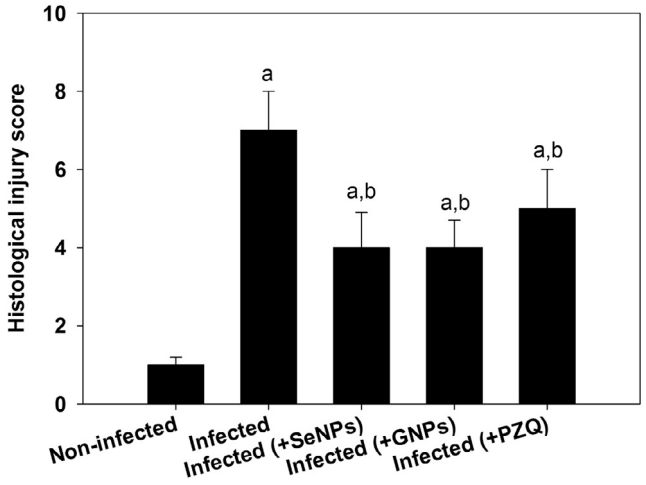

Fig. 4. Effect of SeNPs and GNPs on the jejunum histology score of mice infected with *S. mansoni*. Scores were calculated according to Dommels et al. (2007). Values are means ± SD. [a]Significance against non-infected mice at $p \leq 0.05$. [b]Significance against infected mice at $p \leq 0.05$.

S. mansoni tends to switch from Krebs cycle to lactate production in the host which results in a surplus supply of O_2.

Mahmoud and Elbessoumy (2013) concluded that schistosomiasis induced a significant decrease in GSH level in mice liver, thus serving to decrease the hepatic antioxidant capacity and generating lipid peroxides that may in turn play a central role in the pathology associated with schistosomiasis (Fahmy et al., 2014). Moreover, Gharib et al. (1999) attributed the decreased GSH level to the increased cytotoxicity with H_2O_2 which is produced as a result of inhibition of glutathione reductase that keeps GSH in its reduced form.

On the other hand, treatment with SeNPs and GNPs to schistosome infected mice decreased the jejunal oxidative stress significantly. Our results are in agreement with Dkhil et al. (2015a,b, 2016a,b, 2017), and Bhattacharjee et al. (2017).

According to Dkhil et al. (2015a,b, 2016b, 2017), GNPs showed an anti-neuroschistosomal effect in mice infected with *S. mansoni* where GSH level was elevated significantly in brain, liver, kidney and spleen. Meanwhile, a significant reduction was found in nitrite/nitrate and MDA levels in schistosome infected mice.

In the same line, Dkhil et al. (2015a,b) reported ameliorating effects of GNPs on schistosomiasis-promoted oxidative stress may be attributed to their ability to scavenge free radicals, and that this action could find a clinical use in the treatment of hepatic dysfunction in schistosomiasis.

Likewise, SeNPs have anti-schistosomal activities in liver of schistosome infected mice where; they increased GSH level significantly and reduced nitrite/nitrate and MDA levels significantly Dkhil et al. (2015a,b). Moreover, Bhattacharjee et al. (2017) attributed the restoration of hepatic antioxidant enzyme activity in cyclophosphamide intoxicated mice, and the significant reduction of MDA and reactive oxygen species levels in liver cytosol and bone marrow cells by nanoselenium particles to their protective role in preventing lipid peroxidation and in maintaining the integrity and normal function of the hepatic cells.

Furthermore, SeNPs suppressed the oxidative stress by preventing GSH depletion. It may be possible that treatment with nanoselenium increased the activity of antioxidant selenoenzyme GPx which, in turn, upregulated the other antioxidant enzyme systems (Bhattacharjee et al., 2017).

Our results have shown that schistosomiasis induced a significant increase in mice body weight. Fiore et al. (1996) reported that in schistosomiasis, retention of liquids might follow the ascitic processes, and it was known that water retention result in gain in body weight of mice (Dewar, 1963). However, the treatment of infected mice with NPs of either selenium or gold caused a significant decrease in the body weight compared to the infected animals with *Schistosomiasis mansoni*, and interestingly the change of body weight in animals treated with NPs was non-significant compared to uninfected control group. The non-significant decrease in body weight of infected mice injected with GNPs agrees with the findings of Zhang et al. (2010). The non-significant change of our results on body weight of infected mice treated with metal NPs assures the protective role of SeNPs (Dkhil et al., 2016a) and GNPs (Zhang et al., 2010).

The histopathological evaluation of the intestinal sections of infected mice with no treatment revealed disturbed architectural structure associated with obvious inflammation of the jejunum, and numerous large granulomas mostly with schistosomal eggs were distributed in the mucosa, submucosa and muscularis. These observations were similar to those previously described (Riad et al., 2008; Bauomy et al., 2014).

Production of granulomas in the intestine of infected animals is an inflammatory response due to antigens released by the parasite eggs (Hirata et al., 1993). On the other hand, infected mice treated with NPs of either selenium or gold have shown obvious recovery in the intestinal tissues and granulomas were either few or non-developed; findings which indicate the antischistosomal and anti-inflammatory activities of the nanometals in the intestinal tissue. Antischistosomal influences of both selenium and gold NPs agree with Bayaumy and Darwish (2016), who reported that oral administration of heteropolyoxotungstate nanocomposite to mice infected with *Schistosoma mansoni* have shown diminishment of granulomatous lesions. Additionally, the anti-inflammatory role of NPs in the intestine was previously reported on mice by Laroui et al. (2012), they concluded that low doses of nanoparticles could be used as drugs for treatment of inflammatory

gastrointestinal diseases. Moreover, *in vivo* administration of Poly-(ε-caprolactone) nanoparticles in mice have enhanced the uptake of the nanoparticles via intestinal mucosa and elicited the immune response via production of IgG antibodies in serum (Singh et al., 2006).

Our study was a part of serial studies made by the authors to address the antischistosomal activities of NPs. It revealed that both of SeNPs and GNPs have therapeutic effects against intestinal disorders induced by *Schistosomiasis mansoni*. They reduced the levels of oxidative stress, body weight changes, histological impairment and goblet cells number in the jejunum. These curative influences of NPs are linked with their antioxidant activities; thus, they have proved their potential anti-schistosomal activities in mice successfully.

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