Original Article

Efficacy of Gold Nanoparticles against Nephrotoxicity Induced by *Schistosoma mansoni* Infection in Mice*

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Abstract

Objective In this study, the ameliorative effects of gold nanoparticles (gold NP) on the renal tissue damage in *Schistosoma mansoni* (*S. mansoni*)-infected mice was investigated.

Methods High-resolution transmission electron microscopy was used for the characterization of NP. The gold NP at concentrations of 250, 500, and 1000 μg/kg body weight were inoculated into *S. mansoni*-infected mice.

Results The parasite caused alterations in the histological architecture. Furthermore, it induced a significant reduction in the renal glutathione levels; however, the levels of nitric oxide and malondialdehyde were significantly elevated. The parasite also managed to downregulate *KIM-1, NGAL, MCP-1,* and *TGF-β* mRNA expression in infected animals. Notably, gold NP treatment in mice reduced the extent of histological impairment and renal oxidative damage. Gold NP were able to regulate gene expression impaired by *S. Mansoni* infection.

Conclusion The curative effect of gold NP against renal toxicity in *S. mansoni*-infected mice is associated with their role as free radical scavengers.

Key words: Gold nanoparticles; Schistosomiasis; Renal damage; Gene expression; Histopathology; Oxidative stress

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INTRODUCTION

Schistosomiasis is considered one of the most important water-based tropical diseases that affects the world's poorest people[1]. It is a chronic inflammatory disorder caused by flatworms (or flukes) belonging to the genus *Schistosoma*. This disease threatens about 800 million people worldwide and more than 200 million are infected. The suggested global burden of schistosomiasis is up to 4.5 million disability-adjusted life years[2]. In addition, the general health, growth, cognitive development, and future reproductive health of approximately 60% of African children are adversely affected by the disease[3].

El-Sokkary et al.[3] and Mutapi et al.[4] observed that *Schistosoma mansoni* (*S. mansoni*) infection causes oxidative stress in the kidney, liver, and spleen[4-5]. In addition, epidemiological studies have shown that schistosomiasis is associated with renal injury and renal parenchymal changes, which are mediated by immune complexes[6].

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The treatment and control of schistosomiasis rely almost exclusively on praziquantel (PZQ)[7-8]. However, drug resistance has been an ongoing threat because of the large-scale administration of PZQ[9-10]. Although PZQ has a broad spectrum of activity, its activity is becoming inadequate, showing only moderate activity against immature worms[7]. Therefore, the discovery and development of novel antischistosomal drugs is crucial.

The discovery of new nanosized particles could improve health care in humans[11]. Within the last few years, the Food and Drug Administration has approved the use of nanotechnology-based drugs and its development by several pharmacological companies. Gold nanoparticles (NP) exert therapeutic effects against disorders such as chronic inflammation, rheumatoid arthritis, pathological neovascularization, and neoplasia[12].

Notably, the use of NP has been extended to the control of various pathogens, such as parasites, viruses, and bacteria. Shamaila et al.[13] concluded that gold NP that are 6-40 nm in size exhibited high antibacterial activity, and the antibacterial activity was dependent on size and dose. Tu[14] discovered that plant-borne molecules could be used to synthesize less toxic, effective mosquitocidal NP against young *Aedes*, *Ochlerotatus*, *Anopheles*, and *Culex* instars. Green-synthesized NP have been used as mosquitocides against the vectors of malaria[15-16] and Zika virus[17]. Low doses of lemongrass-synthesized gold NP were observed to enhance the predation potential of freshwater copepod *Mesocyclops aspericornis* (Daday, 1906) on early instar mosquito larvae. This process might help to control the vectors of malaria and dengue[18]. In addition, artificial titanium dioxide NP have shown safer mosquitocidal potential[19].

In our previous studies on the protective effects of NP against hepatic and neural dysfunctions induced by *S. mansoni* infection in mice, gold NP exhibited a dose-dependent curative effect in the infected animals[20-21]. Therefore, the aim of the present study was to evaluate the therapeutic effect of gold NP on renal damage induced by *S. mansoni* infection in mice.

MATERIALS AND METHODS

Experimental Animals

Seventy-two male Swiss albino mice, aged 9-11 weeks, and weighing 20-25 g were maintained under specific pathogen-free conditions, fed a standard diet, and provided with water *ad libitum*. All reagents below were purchased from Sigma-Aldrich (St Louis, MO, USA) unless otherwise specified.

Gold Nanoparticles

Gold NP were prepared by the chemical reduction method[22]. Chloroauric acid ($HAuCl_4$) was used as the Au^{3+} ion precursor, while sodium citrate was used as both reducing and stabilizing agent. The color of the solution slowly turned into faint pink color, indicating the reduction of Au^{3+} ions to Au nanoparticles.

The size and morphology of gold NP were determined by transmission electron microscopy (TEM). The samples for TEM were prepared using a clear solution of NP. The prepared solution was loaded onto a Formvar-coated grid, on which a drop of the sample solution (containing dispersed NP) was placed and allowed to air-dry. Electron micrographs were obtained using a JEOL JEM 2000 EX microscope (JEOL Ltd., Tokyo, Janpan).

Infection of Mice

The mice were injected subcutaneously with 100±10 *S. mansoni* cercariae[23], which were obtained from Schistosome Biological Supply Center, Theodor Bilharz Research Institute (TBRI), Imbaba, Giza, Egypt.

Experimental Design

The animals were allocated to six groups, each comprising 12 mice. The mice in one group were uninfected and received water (100 µL water/mouse) by oral gavage for 10 d. The remaining mice were infected with 100±10 *S. mansoni* cercariae. The infected animals were divided into five groups, 46 d post infection (p.i.). One group was infected and left untreated, while three of the remaining four infected groups received an intraperitoneal (IP) injection of gold NP (100 µL) at 250, 500, and 1000 µg/kg body weight, respectively, on days 46 and 49 p.i. On day 46 p.i., the infected mice in the fifth group were orally administered 100 µL of PZQ ($6x10^5$ µg/kg body weight) every 24 h for 2 d. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. The investigation was conducted in accordance with the legal and ethical guidelines of the Medical Ethics Committee of TBRI, Giza, Egypt (Approval No. 4018/2011).