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Resveratrol ameliorates oxidative stress and organ dysfunction in *Schistosoma mansoni* infected mice

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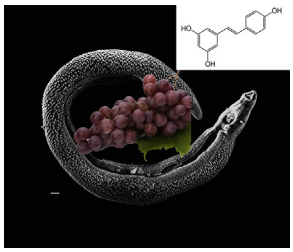
HIGHLIGHTS

- *Schistosoma mansoni* causes oxidative stress in most body organs of infected hosts.
- Resveratrol ameliorates oxidative stress in *S. mansoni* infected mice.
- The antioxidative effect of resveratrol is more pronounced in some organs.

GRAPHICAL ABSTRACT



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ABSTRACT

Schistosoma mansoni causes a major chronic debilitating disease in more than 230 million people around the world. The pathognomonic granuloma is a major cause of the oxidative stress encountered as a consequence of infection not only in the liver, but also in other important organs as spleen, lung, brain and kidney. Resveratrol administration at a dose of 20 mg/kg once daily for two weeks to mice infected with *Schistosoma mansoni* resulted in improvement in serum cholesterol and triglyceride levels. Enzymatic antioxidant profile showed significant modulations in Superoxide dismutase, catalase activities and reduced glutathione levels. Specific biomarkers for homeostasis of brain and lung i.e. Tau and RAGE respectively, showed significant improvement after resveratrol administration.

1. Introduction

Schistosoma is the causative parasite of the debilitating infection schistosomiasis, which affects over 230 million people in 74 endemic countries (Gryseels et al., 2006). Approximately 280,000 deaths annually are linked to schistosomiasis (van der Werf et al., 2003). Morbidity and mortality in schistosomiasis are attributed to an unparalleled form of liver fibrosis. The egg cuticle encloses a miracidium that releases enzymes and antigens via multiple pores. As presumed, the host reacts in a manner that involves reactive oxygen species (ROS) (Caulfield et al., 1985). Moreover, eosinophils, which is one of the components of the *Schistosoma*-induced hepatic granulomas, generate the hydroxyl radical (·OH) and the superoxide anion ($O2^{-}\cdot$) (McCormick et al., 1996).

It is a well-accepted fact that oxidative stress participates in

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schistosomiasis pathogensis mainly through leukocyte activation in response to the parasite presence (Elsammak et al., 2008). Several organs, mainly liver, spleen and kidneys are mostly affected by increased eosinophil peroxidase activity and imbalance in the antioxidant defense mechanisms causing these organs to be shifted to a pro-oxidant state. (Abdallahi et al., 1999; Gharib et al., 1999). Mammalian cells has adopted a chain of antioxidant systems, either enzymatic or not, to limit and overcome the harmful effects imposed by ROS. Enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) are the key players. The SOD hastens the speed of dismutation of superoxide to hydrogen peroxide (H2O2). This enzyme is located both in the mitochondria and in the cytosol as well as in extracellular milieu. Afterwards, comes the action of the CAT which transforms H2O2 into water and oxygen. In addition, selenium peroxidase scavenges both H2O2 and organic hydroperoxides, using as cofactor oxidized glutathione which in turn is converted to reduced glutathione (GSH) by the enzyme glutathione reductase (Chiumiento and Bruschi, 2009). GSH may also act directly as a scavenger of free radicals and/or as substrate for GPxs and Glutathione-S-transferases (GSTs) (Chiumiento and Bruschi, 2009).

RAGE (The receptor for advanced glycation endproducts) is a multi-ligand receptor expressed at high levels in lungs, but it is normally not expressed or found at very low levels in other tissues (Buckley and Ehrhardt, 2010; Creagh-Brown et al., 2010). The high levels of RAGE expression during lung development and in adult pulmonary tissue is connected to its physiological role in lung homeostasis and morphogenesis (Buckley and Ehrhardt, 2010). Decreased RAGE levels are usually accompanied by impairment of lung function related to several diseases (Queisser et al., 2008; Buckley and Ehrhardt, 2010), mostly cancer development and is frequently observed in several lung pathologies such as chronic obstructive pulmonary disease, asthma, and parenchymal lung diseases (Bartling et al., 2005; Franklin, 2007; Queisser et al., 2008).

Tau protein expression and aberrant hyperphosphorylation are nowadays one of the most commonly used markers in the field of neurological pathologies. It is used as a common marker of neurodegeneration and is hugely accompanied with neuronal cell death and neurological impairment in a variety of conditions affecting the CNS, including many infectious diseases and importantly, Alzheimer's disease (Wang et al., 2012). Tau proteins are responsible for microtubule stabilization in neurons. Modifications in the pattern of tau expression and phosphorylation are associated with defective microtubule stabilization resulting in consequent neuronal death (Wang et al., 2012). These biochemical processes is now implicated in conditions collectively denominated "tauopathies", including Alzheimer's disease (Goedert et al., 1998).

Resveratrol (RSV) is a 3, 4, 5-trihydroxystilbene, a naturally occurring polyphenol found in different plant species (Szkudelska and Szkudelski, 2010). Enormous amounts of resveratrol are found in berries, grapes, peanuts and can be used in tablets form as a dietary supplement (Vidavalur et al., 2006). Several studies had investigated its beneficiary health effects on conditions such as atherosclerosis (Wu and Hsieh, 2011), diabetes (Su et al., 2006), and muscular dystrophy (Hori et al., 2011), in addition to its neuroprotective effects (Sun et al., 2010) and cardioprotective effects (Tanno et al., 2010). RSV not only acts as an antioxidant itself, but also induces other intracellular antioxidative activity (Tanno et al., 2010). RSV carries its antioxidant effect by targeting and activating the NAD + -dependent protein deacetylates SIRT1 (silent information regulator (SIR) genes (sirtuin)); in turn, SIRT1 induces an intracellular antioxidative mechanism by inducing mitochondrial superoxide dismutase (SOD) (Tanno et al., 2010).

Most researches concentrate on the liver pathology as the main organ affected by the disease. We expanded to investigate the effect of RSV on ameliorating the oxidative stress imposed on liver, lung, kidney, brain and spleen of mice infected with *schistosoma mansoni*. We also explored the effect of RSV on TAU level in the brain and RAGE level in the lungs of the same study group as more specific markers for the homeostasis of these specific two organs.

2. Materials and methods

2.1. Chemicals

All common chemicals used were purchased from Sigma Co. (St. Loius, MO, USA). RSV powder was purchased from Sigma-Aldrish Chemie (Steinheim, Germany). CAT, SOD & GSH diagnostic kits were purchased from Bio-Diagnostic (Egypt). All PCR reagents were purchased from Roche Diagnostics GmbH (Mannheim, Germany).

2.2. Animals

Male Swiss albino pathogen-free mice (*Mus musculus domesticus*); 4–6 weeks and weighing 18–20 g were used. The animals were provided by the animal house of the Theodor Bilharz Research Institute (TBRI), Giza, Egypt. The mice were maintained on a standard commercial chow *ad libitum* in an air-conditioned animal house at 20–22 °C.

Animals were divided into 3 groups, 10 mice each:

Group 1: negative control group: healthy mice without infection and receiving normal diet.
Group 2: positive control group: mice were infected with *S. mansoni* cercariae through subcutaneous route by 50 ± 10 cercariae per mouse. The animals were placed into cylindrical vials with a thin water layer containing the cercariae for a period of 30 min This group did not receive any medication.
Group 3: RSV group: mice were infected with *S. mansoni* cercariae through subcutaneous route as in group 2 but received RSV as freshly prepared suspension in 0.5% carboxymethyl cellulose in distilled water orally in a dose of 20 mg/kg once daily for 2 weeks after 4 weeks from infection.

All mice were sacrificed at the 8th week post infection, blood samples were collected for biochemical analysis, organs like kidneys, spleens and livers were removed immediately and frozen for subsequent manipulation of enzymatic assays, while lungs and brains were divided first before freezing into two portions: one for the enzymatic assays and the other for the molecular testing.

2.3. Biochemical analysis

Serum samples were collected and stored at−20 °C until used. Total protein levels were measured according to Doumas et al. (1981). Total cholesterol (TC), Triglycerides (TG) were measured according to Richmond (1973), Wahlefeld and Bergmeye (1974) respectively.

2.4. Assay of antioxidant enzymes

2.4.1. Superoxide dismutase assay (SOD)

Superoxide dismutase was assayed spectrophotometrically according to Nishikimi et al. (1972). This assay relies on the ability of the enzyme to inhibit the phenazine methosulphate-mediated reduction of nitroblue tetrazolium dye. Briefly, tissues were homogenized in 100 mM phosphate buffer (pH 7.0) and centrifuged (4000 rpm - 15 min at 4 °C) to remove cellular debris. The inhibition of superoxide-dependent adrenaline auto-oxidation in a reaction buffer was monitored in a spectrophotometer at 560 nm. Results