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Therapeutic effect of *Sepia* ink extract against invasive pulmonary aspergillosis in mice

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Abstract Invasive pulmonary aspergillosis (IPA) is a life-threatening disease in immunocompromised patients that requires aggressive therapy. Because of the widespread use of antibiotics, corticosteroids, antitumor drugs, and immunosuppressive drugs, the morbidity of IPA is currently increasing. The ink secretion of molluscan species was identified as one of the novel sources of bioactive compounds. So the present study designed to investigate the antifungal and antioxidant effects of *Sepia officinalis* ink extract against IPA in mice. Eighty neutropenic infected mice were randomly assigned into four main groups (20 mice/group). The 1st group was treated with saline, neutropenic infected, the 2nd group was treated with ink (200 mg/kg) and the 3rd group was treated with amphotericin B (150 mg/kg) and the 4th group was treated with ink plus amphotericin B (Ink 200 mg/kg and AMB 150 mg/kg). Treatment was started at 24 h after fungal inoculation and was administered for 3 consecutive days. The present study demonstrated good *in vitro* and *in vivo* antifungal activity of IE against *Aspergillus fumigatus*. Compared with IPA group; IE-treated, AMB-treated, and AMB + IE-treated animals had a 67.80%, 83.41%, and 72.68% reduction in the pulmonary fungal burden, respectively. Treatment with IE and/or AMB for one and three days significantly decreased MDA and increased GSH and SOD levels in the lung tissues as compared with the infected untreated group. In conclusion, the results of our *in vivo* and *in vitro* studies demonstrate that IE has therapeutic effect against invasive pulmonary aspergillosis via reducing oxidative stress.
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Introduction

Aspergillosis refers to the spectrum of diseases caused by *Aspergillus* species (Thompson and Patterson, 2008). *Aspergillus fumigates* (*Aspergillus fumigatus*) is the most common species among *Aspergillus*, accounting for 90% of all respiratory infections. *Aspergillus* species enter the host most commonly through the lungs by the inhalation of conidia. However, infection has also been reported by exposure and inhalation of

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water aerosols contaminated with *Aspergillus* conidia (Anaissie et al., 2002). Without effective host defenses following pulmonary exposure, the conidia resting in alveoli begin to enlarge and germinate. Hyphal transformation with vascular invasion and dissemination of infection are potential sequel (Thompson and Patterson, 2008). *A. fumigatus* is responsible for severe and often fatal infections in immunocompromised patients (Das Gupta et al., 2014). Moreover, *A. fumigatus* causes severe pulmonary infections in humans, such as invasive pulmonary aspergillosis (IPA) (Obar et al., 2013).

Invasive pulmonary aspergillosis (IPA) is a life-threatening disease of immunocompromised patients that requires aggressive therapy (Tsuji and Ogawa, 2011; Krel et al., 2014). Cancer chemotherapy and allogeneic bone marrow transplantation are associated with fungal disease, and up to 30% of patients with acute leukemia experience invasive fungal infections. Fungi are one of the most neglected pathogens, as demonstrated by the fact that the amphotericin B (AMB), a polyene antibiotic used for more than 50 years, is still used as a "gold standard" for antifungal therapy (Ostrosky-Zeichner et al., 2003; Gibbs et al., 2005; Chudzik et al., 2013). In neutropenic patients with IPA, treatment with amphotericin B is customary but often ineffective, with reported response rates of less than 55% in leukemia patients and bone marrow recipients (Becker et al., 2003). Antimicrobial resistance, and the resulting failure of antimicrobial therapies in humans, is a mounting public health problem of global significance (Marcos-Zambrano et al., 2014). Moreover, in humans, the most common and dose limiting side effect of amphotericin B is severe nephrotoxicosis (Geo vigila and Baskaran, 2011; Bes et al., 2014).

Because of the widespread use of antibiotics, corticosteroids, antitumor drugs, and immunosuppressive drugs, the morbidity of IPA is currently increasing. Emerging evidence suggests that marine natural products continue to be a major source of nutraceutical and functional foods and as a source material for the development of drugs (Koyama et al., 2006). The cuttlefish *Sepia officinalis* relies for defense on the ejection of a dark ink in order to create a dark, diffuse cloud which can obscure the predator's view, allowing the cephalopod to make a rapid retreat by jetting away. *Sepia* ink consists of a suspension of melanin granules in a viscous colorless medium (Palumbo, 2003). Most of the studies concerning antimicrobial activity include specific compartments like egg masses, hemolymph or whole body extracts of mollusk (Haug et al., 2004). Mollusks not only exhibit the anti-microbial activity, but also constitute many classes of bioactive compounds which include antitumor, antileukemic and antiviral activities (Premanand et al., 1997; Rajaganapathy et al., 2000). It has been reported that, *Sepia* ink extract at the suitable concentration is able to alleviate the *in vivo* immunosuppression induced by cyclophosphamide in mice (Guang et al., 2009). Also, Zhong et al. (2009) studied the protective effects of squid ink extract toward hemopoietic injuries induced by cyclophosphamine.

Reactive oxygen species (ROS) are essential components of the defensive mechanism against fungus infection (Ibrahim-Granet et al., 2003; Noubade et al., 2014). Following inhalation, *A. fumigates* conidia are either phagocytosed by alveolar macrophages or germinate to form hyphae and are then phagocytosed by the second line of defense, the neutrophils (Dagenais and Keller, 2009). Both macrophages and neutrophils mediate powerful fungicidal effects on *A. fumigates* by producing reactive oxygen species (ROS) (Chauhan et al., 2006). Oxidative stress in the lung is induced by the oxidant-antioxidant imbalance; high levels of ROS in macrophages can result in DNA damage, lipid peroxidation, and protein inactivation. The present investigation aims to evaluate the antifungal and antioxidant effects of *S. officinalis* ink extract against IPA in mice.

Materials and methods

Chemicals

Amphotericin B was purchased as Fungizone (E.R. Squibb & Sons, Princeton, NJ). All other chemicals were purchased from local standard companies and were of reagent grade or better.

Preparation of cuttlefish ink extract (IE)

The cuttlefish ink extract (IE) was prepared according to our previous study, Fahmy et al. (2014). In brief, fresh cuttlefish (*S. officinalis*) were purchased directly from a fishmonger and rapidly transferred to the laboratory where they were dissected and the ink was collected and diluted immediately with an equal volume of dist. water and ground sufficiently. The admixture was collected immediately, concentrated and lyophilized to a black residue using LABCONCO lyophilizer, shell freeze system, USA.

Free radical scavenging activity

The free radical scavenging activities of the extract and vitamin C were analyzed by the DPPH assay (Sanchez-Moreno et al., 1998). A 1.0 ml of the test extract, at gradient final concentrations of 10–80 mg/ml, was mixed with 2 ml of 0.3 mM DPPH solution in MeOH in a cuvette. The absorbance was taken at 517 nm after 20 min of incubation in the dark at room temperature. The experiment was done in triplicates. The percentage antioxidant activity was calculated as follows:

$$\%\text{Antioxidant Activity [AA]} = 100 - \left[\{(\text{Abs}_{\text{sample}} - \text{Abs}_{\text{blank}}) \times 100\} / \text{Abs}_{\text{control}}\right].$$

where $\text{Abs}_{\text{sample}}$ was the absorbance of sample solution (2.0 ml) + DPPH solution (1.0 ml, 0.3 mM), $\text{Abs}_{\text{blank}}$ was the absorbance of methanol (1.0 ml) + sample solution (2.0 ml), $\text{Abs}_{\text{control}}$ was the absorbance of DPPH solution (1.0 ml, 0.3 mM) + methanol (2.0 ml).

Test organism and growth conditions

A strain of *A. fumigates* isolated from an immunocompromised patient with IPA served as the parental strain in this investigation. A working culture of this strain was maintained on peptone yeast extract glucose (PYG: peptone 1 g; yeast extract 1 g; glucose 3 g; per liter of distilled water) agar slants at room temperature. For the preparation of conidial suspension, a culture of *A. fumigatus* was grown on PYG agar for 6 days at 35 °C, and the conidia were collected as described previously (Manavathu et al., 1999).

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