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ORIGINAL ARTICLE

# Biological effects of *Naja haje* crude venom on the hepatic and renal tissues of mice

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**Abstract** Snake venoms are known to cause different metabolic disorders, altering cellular and enzymatic activities in animals and releasing pharmacological substances. In this study, the lethality as well as biochemical and histopathological effect of Egyptian cobra (*Naja haje*; *N. haje*) crude venom at a sublethal dose have been investigated on liver and kidney of male mice. Venom injected intramuscularly in mice with 1/2 LD50 (approximately 0.0115 μg/g body weight of mice) and the animals were sacrificed 6 days post injection. Results indicated that the injection of crude venom of the *N. haje* induced a significant disturbance in liver and kidney functions. In addition, results revealed that *N. haje* venom has a potent oxidative activity by increasing the level of reactive oxygen species with concomitant significant increase in hydrogen peroxide, lipid peroxidation, carbonyl protein and nitric oxide levels in hepatic and renal tissues. This activity was extended to decrease non-enzymatic and enzymatic antioxidant defense components such as glutathione, superoxide dismutase and catalase. Additionally, the biochemical alternations induced in hepatic and renal tissues were associated with significant alternations in the histological architecture of liver and kidney of

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injected mice. From this study, we can conclude that such injury could be considered among the factors that lead to death caused by *N. haje* venom.

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## 1. Introduction

The study of structure and function of snake venom toxins is carrying out with medical application purposes. Snake venom is a complex mixture of many substances, such as toxins, enzymes, growth factors, activators and inhibitors with a wide spectrum of biological activities (Rahmy and Hemmaid, 2000; Al-Sadoon et al., 2013; Cherifi and Laraba-Djebari, 2013). They are also known to cause different metabolic disorders by altering the cellular inclusions and enzymatic activities of different organs (Aiesenberg, 1981). Cobra snakes are widely distributed in Africa and the Middle East. In Egypt, family Elapidae includes several toxic species of snakes, among which is the Egyptian cobra, *Naja haje*. In Egypt, *N. haje* distributes in Nile Valley and Delta, Faiyum and Western Mediterranean Coastal Desert. Envenomation causes local pain and swelling, and may be associated with blistering at the bite site. Neurotoxic and systemic symptoms develop within few hours, and deaths have occurred within 6–16 h after large snakes' bites, despite the use of antivenom and mechanical ventilation. Cobra envenoming is known to induce multiple-organ failure, leading to death in case of severe envenoming (Cher et al., 2005).

Liver is considered as one of the targets for cobra venom factor (Fu et al., 1997). Hepatic injury due to cobra envenoming was reported by Rahmy and Hemmaid (2000) and Adzu et al. (2005). Doley and Mukherjee (2003) reported that the non-toxic phospholipase A2 isolated from the venom is responsible for inducing liver tissue damaging activity. In addition to hepatotoxicity, nephropathy induced by cobra was mentioned. In a previous study, a sub-lethal dose of the Egyptian cobra venom was found to induce a deleterious action on the histological and histochemical patterns of animal renal tissues. The histological alterations recorded in the tubular epithelial lining cells of most of the cortical renal tubules in all the envenomed mice with cobra venoms were previously reported by Rahmy and Hemmaid (2001) and Sitprija (2006). On reviewing the literatures, it was found that few studies were performed on the biochemical effects of the venom of *N. haje* snake, which is one of the most diverse and widespread genus of cobras.

Thus, the present study aimed to detect the hepatotoxic and nephrotoxic effects of a single dose of the venom of such snake after 6 days of envenomation from the biochemical point of view in relation to induce histopathological damages post cobra envenomation.

## 2. Materials and methods

### 2.1. *N. haje* venom preparation and lethality

Crude venom was obtained from *N. haje* snakes collected from the West Delta of Egypt. In VACSERA laboratory; snake venom was milked, lyophilized, stored in a desiccator at 4 °C in the dark and reconstituted in saline solution prior to use. LD50 of crude venom was determined as described by Meier and Theakston (1986). Briefly, LD50 of the venom was determined by intravenous injection of different concentrations of venom in 0.2 ml of physiological saline into the tail vein of albino mice. Four mice were used per group for each dose. Venom dose of each group was increased by 1 μg venom protein until 50% mortality was observed within 24 h. The LD50 of venom was found to be 0.023 μg/g of mice body weight.

### 2.2. Experimental design

Thirty adult male Swiss Albino mice weighing 22 ± 5 g were used. Animals were selected from the Animal house facility of research institute of ophthalmology, Egypt. Animals were housed in standard condition and fed with normal diet and water *ad libitum*. The experiments were approved by the state authorities and it followed the Egyptian rules on animal protection.

Animals were divided into two groups of 15 mice per group. The first group was injected intramuscularly (i.m.) with 200 μL physiological saline (0.9% NaCl) solution and the second group was injected intramuscularly with 1/2 LD50 (0.0115 μg/g b.wt.) of *N. haje* crude venom in 200 μL saline solution at a single dose.

Animals of both groups were sacrificed at the 6th day post-crude venom injection. Blood samples were collected, centrifuged at 500*g* for 15 min at 4 °C to separate serum and stored at −40 °C until liver and kidney function analysis. Livers and kidneys were weighed and divided into two parts. The first part is for histological studies and the second part for biochemical determinations.

### 2.3. Histological studies

Pieces of liver and kidney were quickly removed, fixed in 10% neutral buffered formalin, dehydrated, embedded in wax and 4- to 5-μm paraffin sections were cut and stained with hematoxylin and eosin. Histological damage in liver and kidney was scored as follows: 0: absent; +: mild; ++; moderate; +++: severe (Jamshidzadeh et al., 2008). The liver activity index was estimated using a modified quantitative Ishak Scoring System (Ishak et al., 1995); scores of 1–3 were assigned to cases of minimal liver damage, scores of 4–8 to mild, scores of 9–12 to moderate and scores of 13–18 to severe cases.

### 2.4. Liver and kidney functions test

Colorimetric determination of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was estimated by measuring the amount of pyruvate and oxaloacetate respectively produced by forming 2,4-dinitrophenylhydrazine, according to the method of Reitman and Frankel (1957). The color of which was measured at 546 nm. L-γ–glutamyl transferase (γGT), uric acid (UA), blood urea nitrogen (BUN) and serum creatinine (Cr) were assayed in serum using kits provided from Biodiagnostic Co. (Giza, Egypt).

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