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Research Article

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Impact of two Egyptian scorpion venoms on blood biochemistry during rat colon carcinogenesis

Sara O. Radwan*, Wesam M. Salama, Elsayed I. Salim

Department of Zoology, Research Lab. of Molecular Carcinogenesis. Faculty of Science, Tanta University, Tanta 31527, Egypt

***Corresponding author**: Sara O. Radwan **e-mail**: sara.osama.radwan@gmail.com
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KEY WORDS

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ABSTRACT

The potential efficacy of two Egyptian scorpion species venoms, *Leiurus quinquestratus* and *Androctonus bicolor* was assessed in relation to hematological and biochemical parameters during the stages of chemically induced rat colon carcinogenesis. Fifty-five, 6-7-week-old male Sprague-Dawley rats weighing 120-125 gram were randomly divided into four groups: As a normal control, group 1 (10 rats) injected subcutaneous (s.c.) and intraperitoneal (i.p.) with saline only. From week 1 to week 4, groups 2, 3, and 4 received 1,2-dimethylhydrazine (40mg/kg/bw) weekly through s.c. injections. Groups 3 and 4 (15 rats per group) received i.p. injections of 1/20 of LD_{50} from either *L. quinquestratus* (LQV) or *A. bicolor* (ABV) venoms from week 5 until the end of the experiment after 16 weeks. Rats were sacrificed following a 16-week experiment. Plasma and sera were collected from each rat's abdominal aorta. Significant alterations were observed in the hematological and biochemical liver and kidney parameters, in rats in treated groups administered (LQV) or (ABV) venoms. To sum up, the use of venoms isolated from *L. quinquestratus* or *A. bicolor* enhanced biochemical and hematological parameters during the colon carcinogenesis process.

Introduction

Colorectal cancer (CRC), commonly known as colon cancer, is a dangerous illness that can influence lifestyle decisions. According to (**Siegel et al., 2023**) it ranks second on the list of causes of death in the US. Research has shown a connection between diabetes mellitus and an individual's age, sex, colon polyps, inflammatory bowel disease, and a higher risk of colorectal cancer **(Sawicki et al., 2021)**. Moreover, a considerable portion of the genesis of colorectal cancer is due to lifestyle factors. Research has shown that physical inactivity, alcohol intake, cigarette smoking, red and processed meat consumption, low-fiber foods, fruits, vegetables, calcium, and nutritional products, as well as being overweight or obese, are risk factors for colorectal cancer **(Sawicki et al., 2021)**. According to **(Chen et al., 2021)** surgery and chemotherapy are the two most effective therapeutic techniques. Many studies have addressed the fact that several chemotherapy medications exhibit a wide range of adverse effects in addition to their potent cytotoxic effects **(Ahmed et al., 2022)**. This is the reason why a growing body of research has demonstrated that nature provides a wide range of bioactive compounds with possible medical uses **(Damavandi et al., 2023).** According to **(Barzkar et al., 2024)**, using natural anticancer drugs has a lot of potential for effective cancer therapy. To identify new therapeutic prospects, natural materials derived from a variety of plant and animal species are crucial. Spiders, ants, wasps, beetles, scorpions, snakes, and caterpillars are just a few of the many species whose venoms contain anticancer properties **(Moran et al., 2022)**. The venom of scorpions is one of the most complex mixtures of non-protein (inorganic salts, lipids, nucleotides, free amino acids, and water) and protein (enzymes and peptides) compounds produced by the venom gland for defense and prey capture **(Evans et al., 2020)**. **(Salman et al., 2017)** claim that BPF directly promotes platelet synthesis and proliferation, which could account for the significant rise in platelet counts observed in rats given BPF following radiation therapy. Also, granulocyte counts rose in mice administered *A. australis* venom, according to **(Nafie et al., 2020)** indicating that the venom might serve as a barrier to safeguard the haemopoietic system. Seven species of the Buthidae family and one species of the Scorpionedae family can be found in Egypt. Accordingly, we carried out this study to evaluate the effects of the

venoms of two Egyptian scorpions, *L. quinquestratus* (LQV) and *A. bicolor* (ABV), on hematological and biochemical parameters throughout the phases of chemically induced rat colon carcinogenesis.

Materials and Methods

Collection of scorpions and venom preparation

One hundred scorpions from two Egyptian species were collected in August 2022 by experienced hunters from the northern Mediterranean coast *Androctonus bicolor* (ABV) or the Aswan region of Upper Egypt *Leiurus quinquestratus* (LQV). Following a careful examination and precise classification, two containers containing various species of scorpions were filled. The samples were milked employing 12 V of electrical stimulation. Before being used, the venom of LQ and AB were centrifuged, lyophilized, and kept at -20 °C **(Salama and Sharshar, 2013)**.

Medium-term colon carcinogenesis rat assay

The care of animals

Fifty-five male Sprague-Dawley rats, approximately six to seven weeks old, 120–125 kg. b.wt., were purchased from Vacsera. They were kept in groups at 23 ± 2 ºC and 55 ± 5% relative humidity for a week after being housed in the animal facility's settings. Daily observations were made on the animals' body weights, amounts of food and drink consumed, and general health. The animals were handled according to the ethical guidelines approved by the animal care and use committee, Faculty of Science, Tanta University (Protocol number: IACUC-SCI-TU- 0270).

Experimental design

Utilizing our most recent study (Unpublished data) estimating the LD_{50} doses of ABV and LQV in male Sprague Dawley (SD) rats, we investigated the potential impact on rat colorectal carcinogenesis of 1/20 of LD_{50} of both venoms. Fifty-five, rats were divided into four groups: Group (Gp)1 (10 rats), was the normal control group (0.9% saline). Group 2, 15 rats received 40 mg/kg b.wt. of 1,2-dimethylhydrazine (DMH), subcutaneous (s.c.) once a week for four consecutive weeks starting from week 1 to week 4 and worked as the carcinogen-only control group. Group 3, after s.c. DMH administration, 15 rats intraperitoneally (i.p.) received the LQV at 1/20 from LD_{50} dose starting from week 5 till the end. Group 4, after s.c. DMH administration, 15 rats received the ABV at 1/20 LD_{50} dose i.p., starting from week 5 to the end. Animals were sacrificed after 16 weeks.

Preparation of blood and serum samples

After overnight fasting and diethyl ether anesthesia, all of the animals were sacrificed at the end of the 16-week trial.

Plasma and sera were collected from each rat by extracting blood from its abdominal aorta into two glass tubes, one of which was heparinized and the other non-heparinized. Using automated techniques, the obtained blood samples' complete blood picture (CBC) was determined. The data included hematocrit, platelets (PT), red blood cells (RBCs), white blood cells (WBCs), hemoglobin (HB) levels, and packed cell volume (PCV) levels. For fifteen minutes at 3000 rpm, centrifugation was utilized to separate the sera. The serum sample was stored at -20 °C until it was used for the biochemical examination of total protein, albumin, Alanine aminotransferase (ALT), Aspartate transaminase (AST), low-density lipoprotein (LDL-C), High-density lipoprotein (HDL-C), urea, creatinine, cholesterol (CHO), triglyceride (TG), blood urea Nitrogen (BUN), and total bilirubin (TB).

Methods

For hematological and serum biochemical investigations, the Dirui BCC-3600 automated hematology analyzer was used to automatically compute for hematological and serum biochemical investigations. A commercial kit (Glutamate Oxaloacetate Transaminase) from DIALAB GmbH-Vienna, Austria (modified IFCC) was used to quantify the amount of AST activity in serum. (ALT) was determined using the methods of **(Thefeld et al., 1974)** and **(Thomas, 1998)**. The methods of **(Thefeld et al., 1974)** and **(Rej, 1984)** were used to calculate (AST). It was used to assess serum total bilirubin, according to **(Tolman and Rej, 1999)**. Following **(Thomas's, 1998)** approach, a commercial kit (Urease/GLDH) supplied by DIALAB GmbH-Vienna, Austria, was used to analyze the amount of urea in serum. The creatinine in serum test was conducted using the approach of **(Parsons and Newman, 1999)**. Using a quantitative kit (Linear Chemicals, S.L., Spain), the serum total cholesterol was measured according to the **Allain et al., (1974)** method. Triglycerides were measured using the technique established by **(Fossati and Prencipe, 1982)**. According to **(Burstein et al., 1970)** and **(Lopez-Virella et al., 1977)** serum HDL-C levels can be measured. Using **(Friedewald et al., 1972)** LDL-C was computed.

Statistical analysis

The ANOVA test was utilized to analyze group data presented as means ± S.D. and Chi-squared (X) data expressed as percentages using the Statistical Package for Social Science (SPSS) version 17.0, USA. A statistical analysis was deemed significant in this study if P was less than 0.05.

Results

Effect of LQV and ABV on complete blood count

The hematological parameters on the blood count of tested rats in all groups are shown in **Table (1)**. Two venoms' effects on blood counts were noted, with a drop in both WBC and RBC in Gp2 which was treated with DMH compared with control Gp1, while Gp3 or Gp4 which were treated with LQV or ABV, respectively, increased compared with Gp2, while PCV decreased in Gp2 compared with the control group, while Gp3 or Gp4 began to increase to approach the normal one compared with Gp2, while MCV and MCH increased in Gp2 compared with the control group while decreased in Gp3 and Gp4 compared with Gp2. While MCHC showed no change in Gp2 or Gp3 but was slightly reduced in Gp4 compared with Gp2, PT was reduced in Gp2 compared with the control group and also reduced in Gp4 compared with Gp2, while there was a significant increase in Gp3 compared with the other Gp1, Gp2, and Gp4. Lymphocytes decreased in Gp2 compared to the control group while increasing in Gp3 and Gp4 compared to Gp2. While monocytes increased in Gp2 compared to the control group, in Gp3 and Gp4, they decreased compared to Gp2. Finally, neutrophils increased in Gp2 compared to the control group, while they significantly increased in Gp3 and Gp4 compared to Gp2. After the investigation, the hematological parameters showed that LQV or ABV may protect the hematopoietic system because they try to approach the normal range either by decreasing or increasing.

Table (1): Effect of two venoms LQ and AB on the hematological parameters

Group/Treatment (Unit)	Gp1 (Control)	Gp2 (DMH)	Gp3 (DMH+LQV)	Gp4 (DMH+ABV)
WBC ($X10^3/\mu L$)	15.8 ± 6.1	7.9 ± 4.1*	10.6 ± 1.4**	12.5 ± 2.1**
RBC ($X10^6/Ml$)	7.2 ± 0.1	6.5 ± 0.5	7.4 ± 0.3	7.3 ± 0.3
HB (g/dl)	14.0 ± 0.1	13.0 ± 0.7	13.2 ± 1.2	13.9 ± 0.5
PCV (%)	38.7 ± 0.1	36.1 ± 2.5	36.4 ± 1.9	39.6 ± 1.6
MCV (fl)	53.8 ± 0.9	55.7 ± 0.3*	49.4 ± 1.3	54.6 ± 1.8
MCH (pg)	19.4 ± 0.5	20.1 ± 0.6	18.0 ± 1.0	19.2 ± 0.8
MCHC (g/dl)	36.1 ± 0.3	36.1 ± 0.8	36.2 ± 1.6	35.1 ± 0.5
PLT ($X10^3/\mu L$)	786.5 ± 3.5	779 ± 117.9	935.3 ± 82.1*, **	766 ± 139.3
LYM ($X10^3/\mu L$)	88.0 ± 3.0	80.7 ± 7.1	81.3 ± 1.9	82.0 ± 7.1
MONO ($X10^3/\mu L$)	8.0 ± 2.0	12.0 ± 2.5*	9.3 ± 0.5	10.0 ± 2.2
NEUT ($X10^3/\mu L$)	4.0 ± 1.0	7.3 ± 4.8*	9.3 ± 2.4*, **	8.0 ± 5.0*, **

Values are means ± S.D. (for five determinations); WBC, white blood cell; RBC, red blood cell; HB, hemoglobin; PCV, packed cell volume; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; PLT, platelets count; LYM, lymphocyte; MONO, mean monocyte; NEUT, mean Neutrophils; g/dl (grams per deciliter); fL (femto liters); pg (picograms); *: Significant vs. Gp1. **: Significant vs. Gp2.

Effect on liver function parameters

The effects of liver function parameters on each group of rats are shown in **Fig. (1)**. Gp2 had an increase in TB as compared to the control, but Gp3 and Gp4 decreased in comparison to Gp2. Group 2 displayed no change in DB when compared to Gp1. Gp3 exhibited a decrease when compared to Gp2, while Gp4 showed no change. Gp2 exhibited a rise in ALT as compared to the control group, whereas Gp3 demonstrated a noteworthy increase and Gp4 demonstrated a decrease. AST rose in the Gp2 compared to the control group, but it decreased in the Gp3 group and increased noticeably in Gp4. In Gp2 and Gp3, the total protein did not alter; in Gp4, it did. On the other hand, ALB remained constant in all groups.

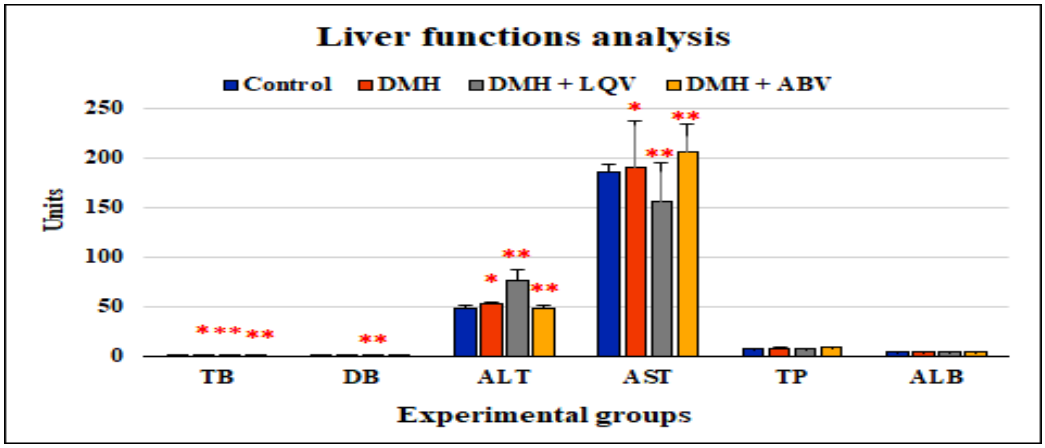

Fig. (1): Illustrates changes in TB: total bilirubin; DB: direct bilirubin; ALT: Alanine transaminase; AST: Aspartate amino TP: total protein and ALB: albumin in studied groups; Gp1: normal control; Gp2: treated with DMH-only; Gp3: DMH+LQV; and Gp4: DMH+ABV. *: Significant vs. control (Gp1). **: Significant vs. Gp2.

Effect on serum kidney function parameters

Fig. (2) shows that blood levels of urea and creatinine, as well as BUN concentrations, were assessed in all groups as indicators of renal function in tested rats. Whereas urea in Gp2 decreased in comparison to the control group, it increased in Gp3, and it remained unchanged in Gp4 in comparison to Gp2. Gp4 shown a considerable drop in creatinine when compared to the normal group, but Gp2 and Gp3 observed a decline. Gp2 showed a decrease in BUN when compared to the control group, but it increased in Gp3, and there was no change in Gp4 when compared to Gp2. The LQV is attempting to converge on the normal range, as seen by its growing level.

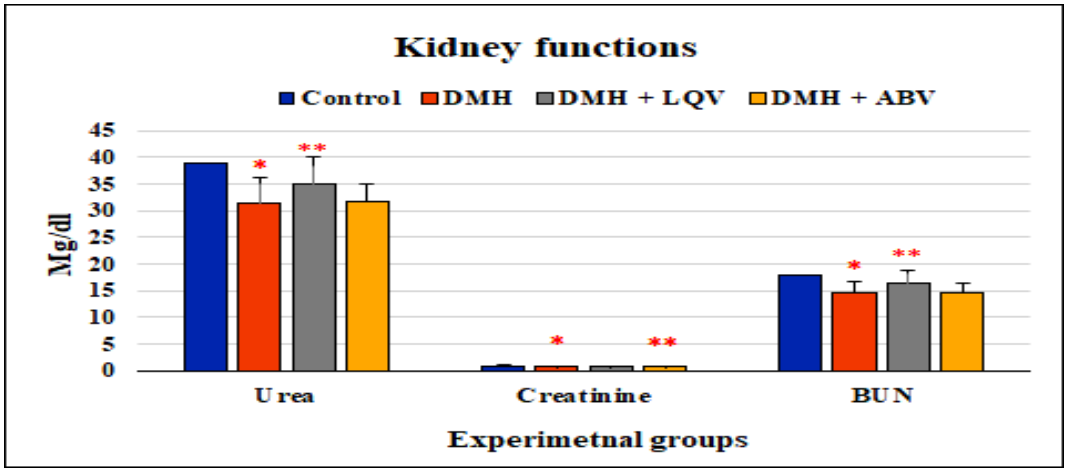

Fig. (2): Illustrates changes in urea, creatinine and BUN in treated groups; Gp1: normal control; Gp2: treated with DMH-only; Gp3: DMH+LQV; and Gp4: DMH+ABV. *: Significant vs. control (Gp1). **: Significant vs. Gp2.

Effect on serum lipid function profile

Two venoms, LQ and AB, were found to have an effect on each group's serum lipid profiles. Gp2 (CHO) was found to be lower than that of Gp1, however, Gp3 and Gp4 CHO were significantly higher than that of Gp2. (TG) in Gp2 were also greater than in Gp1, but TG in Gp3 and Gp4 was lower than in Gp2. (HDL-C) rose in Gp3 and Gp4 but decreased in Gp2 as compared to the control group. (LDL-C) levels varied between groups; Gp2 had lower levels than Gp1, Gp3 had lower levels than Gp2, and Gp4 had greater levels than Gp2. The two venoms may also be trying to get closer to their typical ranges, as indicated by **Fig. (3)**, if their parameters show either a rise or decrease

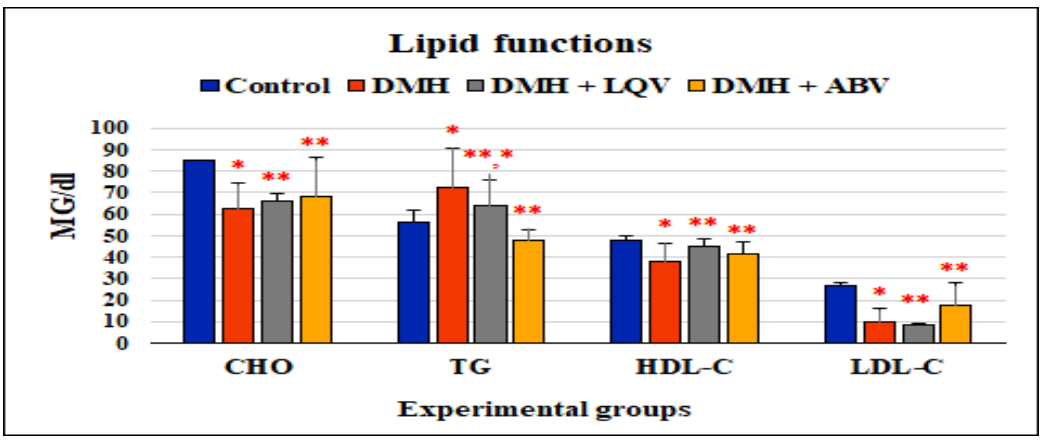

Fig. (3): Illustrates changes in CHO: Cholesterol; TG: Triglyceride; HDL-C: High density lipoprotein; LDL-C: Low density lipoprotein in studied groups; Gp1: normal control; Gp2: treated with DMH-only; Gp3: DMH+LQV; and Gp4: DMH+ABV. *: Significant vs. control (Gp1). **: Significant vs. Gp2.

Discussion

Anemia and myelosuppression are two of the most dangerous adverse effects of cancer treatment. According to **(Jamwal et al., 2020)** anemia in tumor-bearing rats is characterized by lower hemoglobin levels or red blood cell counts and can be induced by hemolytic or myelopathic illnesses. The present study's DMH group exhibited reduced HB levels, WBC counts, RBC counts, and granulocytes; in contrast, the LQV or ABV increased the RBC and WBC counts. The DMH group's greater total differential leukocyte count may have resulted from pressure from the cancer cells' ongoing growth or from an early inflammatory response **(Schoenberg et al., 2022)**. The LQV caused a discernible rise in platelet count. Likewise, **(Salman et al., 2017)** discovered that rats given bradykinin-potentiating factor (BPF) isolated from scorpion venom (*L. quinquestriatus*) following radiation therapy exhibited a significant rise in platelet counts, which could be attributed to BPF directly stimulating platelet synthesis and proliferation. Given that LQV and ABV increased the number of granulocytes, scorpion venom had an immunostimulant effect on tumor cells, suggesting that the venom treatment may initiate an inflammatory response. Studies on hematological traits indicate that the two venoms may operate as a barrier to protect the hematopoietic system. According to **(Nafie et al., 2020)** administering *A. australis* venom to mice had similar results as this study. Based on established hematological traits, the findings indicated that the venom might shield the hematological system. **(Cusinato et al., 2010)** reported that after administration of *Tityus serrulatus* venom (TsV) to Wistar rats, hemoglobin levels increased in terms of hemocrit, red blood cell count, and hemoglobin concentration, which is consistent with our results and suggests that the venom therapy may trigger an inflammatory response. In blood serum, AST and ALT are the two most prevalent liver enzymes. According to **(Zhou et al., 2020)** their serum levels are predictive of some malignancies, including pancreatic and breast cancer, as well as damage and death to liver cells. ALT and AST enzyme activity were found to be correlated with decreased levels of total protein and albumin, suggesting that hepatic dysfunction may be associated with cancer **(Saad et al., 2017)**. As per the findings of this study, the DMH group had higher levels of total protein and albumin, as well as raised ALT and AST values, which were indicative of liver dysfunction and injury due to DMH. While the ALT level in LQV was significantly increased while in ABV

was similar to the normal control group and the AST level in ABV was significantly increased, while in LQV was decreased compared to the DMH group and normal control group, the total protein in ABV was slightly increased while LQV was slightly decreased compared to DMH to approach the normal one, but in albumin, there was a slight decrease after treatment by LQV or ABV also to approach the normal one, which indicates that liver functions were still affected by the carcinogen substance. As opposed to **(Fawzy et al., 2023)** who found that the Smp24 peptide extracted from scorpion venom cured mice by increasing albumin and total protein levels while decreasing ALT and AST levels. In addition, the DMH group's BUN, creatinine, and urea levels were lower than those of the normal control group, according to our present data. Although the creatinine level did not change, the LQV treatment group's urea and BUN levels were greater than those of the DMH group and were nearly within permissible limits. Urea and BUN levels increased somewhat while creatinine levels decreased when comparing the DMH group's treatment to that of the ABV group. Therapy with *A. australis* venom was found to gradually restore the increased levels of urea and creatinine to around normal levels compared to the EAC group, as reported by **(Nafie et al., 2020)**. In the DMH group, the current study found that serum cholesterol, HDL-C, and LDL-C levels fell, whereas triglyceride levels increased significantly. Serum cholesterol and HDL-C levels increased while triglyceride levels decreased in both LQV and ABV. Although the LDL-C level in AB venom was higher than the LDL-C level in LQ venom, the triglyceride level in LQV was significantly higher than that of the control group. Yet, HDL-C rose and grew closer to normal in the LQV and ABV-treated groups of rats as compared to the DMH-treated rats. According to **(Bergelson, 1989)** this indicates that LQV and ABV cause the release of prostaglandins, which may have an impact on cholesterol homeostasis. While serum cholesterol was higher in the two venoms—the AB and the LQ—than in the DMH group, it was still lower than in the normal range. Consequently, the venoms, either LQV or ABV, brought the elevated triglyceride levels and the lowered cholesterol, HDL-C, and LDL-C levels back to roughly normal in comparison to the DMH group. According to **Salman et al. (2017)** rats given BPF following radiation therapy exhibited a noteworthy decrease in their LDL-C, triglyceride, and total cholesterol levels. When irradiated untreated mice were compared to those

treated with BPF (a peptide derived from the venom of the *L. quinquestriatus* scorpion), the HDL-C levels in the former group were significantly greater. LQV is known to possess a high proportion of serotonin, as described by **(Levine et al., 1964)**. Additionally, reports by **(Ismail et al., 1972)** indicate that LQ scorpion venom releases catecholamines. However, by mainly acting on sodium channels, scorpion venom is known to stimulate the release of many neurotransmitters, such as noradrenaline and adrenaline **(Mendes et al., 2023)**. Thus, the following mechanisms of this activity are postulated: insulin resistance; suppression of insulin secretion; peripheral and central stimulation of the adrenergic system; and activation of b-receptors with release of catecholamines and serotonin **(Zare et al., 1994)**. Therefore, it is possible that the elevated blood cholesterol levels in LQV or ABV observed in this study are the consequence of hepatocyte injury that inhibits them from phosphorylating the elevated fatty acid levels, leading to a fatty liver and a modification in the composition of cell membranes Thereby producing neutral fat and phospholipids. **(El-Asmar et al., 1979)**. The free fatty acids generated by the venom would therefore cause acetyl CoA to rise. This increase may lead to an increase in cholesterol production **(Ashmore and Weber, 1968)**. Moreover, after the venoms of LQV and ABV were administered, the amount of free fatty acids increased significantly and the level of triglycerides decreased. The most current results concurred with the previous reports **(Radha et al., 1992)**. Moreover, investigations conducted in vitro and in vivo have confirmed the catecholamines' stimulatory effect on the breakdown of triglycerides **(Fatani, 2010)**.

Summary and recommendations

During the stages of chemically induced colon carcinogenesis, this study shows that treatment with LQV and ABV, changed levels counts by either increasing RBCs or Hb or decreasing HDL-C and LDL-C parameters and so on. Additionally, the two venoms attempted to approach their normal limits in hematological parameters, which could act as a buffer to protect the hematopoietic system. Due to the fact that anemia and myelosuppression are thought to be the most serious side effects of cancer treatment, including scorpion venom in a patient's treatment plan may be a beneficial therapeutic approach.

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تأثير نوعين من سموم العقارب المصرية على الكيمياء الحيوية للدم خلال مراحل تسرطن القولون المستحث في الجرذان

سارة اسامة رضوان*، وسام محمد سلامة، السيد إبراهيم سالم

جامعة طنطا، كلية العلوم، قسم علم الحيوان

تم تقييم الفعالية المحتملة لسم نوعين من العقارب المصرية، *اللوريس كوين كونستراتس والاندروكتونس باي كالر* فيما يتعلق بالمعايير الدموية والكيميائية الحيوية أثناء مراحل تسرطن القولون المستحث كيميائيًا في الجرذان. تم تقسيم خمسة وخمسين جرذا ذكرًا من نوع سبراج داولي، تتراوح أعمارهم بين 6 ل 7 أسابيع، ويزن كل منها ١٢٠ إلى 125 جرامًا، بشكل عشوائي إلى أربع مجموعات: كمجموعة تحكم طبيعية، تلقت المجموعة الاولي (10 جرًذا) محلول ملحي فقط. بدءًا من الأسبوع الاول حتى الأسبوع الرابع، تلقت المجموعات الثانية والثالثة والرابعة حقنًا أسبوعية تحت الجلد من 1 -2 ثنائي ميثيل هيدرازين 40 مجم / كجم / وزن الجسم. من الأسبوع الخامس وحتى انتهاء التجربة بعد 16 أسبوعًا، تلقت الجرذان في المجموعتين 3 و4 (15جردًا لكل مجموعة) حقنًا داخل الصفاق بمقدار 1 /20 من الجرعة الدون مميته من سم عقرب *اللوريس كوين كونستراتس* أو من سم عقرب *الاندروكتونس باي كالر*. تم التضحية بالجرذان بعد تجربة استمرت 16 أسبوعًا. تم جمع البلازما والمصل من الشريان الأورطي البطني لكل جرذ. ولوحظت تغييرات كبيرة في المعايير الدموية والكيمياء الحيوية للكبد والكلى في الجرذان في المجموعات المعالجة التي تم إعطاؤها سموم *اللوريس كوين كونستراتس* أو *الاندروكتونس باي كالر*. وباختصار، أدى استخدام السموم المعزولة من *اللوريس كوين كونستراتس والاندروكتونس باي كالر* إلى تعزيز المعايير الكيميائية الحيوية والدموية أثناء عملية تسرطن القولون.