RESEARCH ARTICLE

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Protective Role of Bee Venom (*Apis mellifera*) Against Kidney Damage in Female Mice with Cancer

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Abstract

Background: Cancer is a dreadful disease that has a huge, negative impact on people's personal, social, and financial lives, as well as their healthcare. The purpose of our study is to evaluate the capability of *Apis mellifera* (A.M.), to reduce the renal toxicity and tissue damage caused by the Ehrlich ascites carcinoma (EAC) in mice. **Methods:** A total of forty female Swiss albino mice were divided evenly among four groups (G1, control; G2, A.M.; G3, EAC; and G4, EAC+ A.M.). **Results:** The current results revealed that EAC caused renal tissue damage, and increase in the serum urea, creatinine, potassium, and chloride ion levels. They also caused a significant decrease in the levels of sodium and calcium ions in the blood, as compared to the normal control. Furthermore, EAC caused a variety of pathological alterations in the glomeruli and renal tubules, including mild glomerular shrinkage, notable cellular infiltration, marked renal injury, and marked renal tissue degradation. When EAC was treated with A.M. (EAC+ A.M.), the kidney structure and function improved, in comparison to the use of EAC alone. The serum urea, creatinine, potassium, and chloride ion levels decreased, but the sodium and calcium ion levels increased. **Conclusion:** It was possible to conclude that A.M. could shield the kidneys from renal toxicity caused by the EAC cells.

Keywords: EAC- venom (*Apis mellifera*)- creatinine- urea- Na+ - K+ - Ca++ - Cl- - Mice

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Introduction

Cancer is a dreadful illness that has had terrible detrimental effects on the social, economic, and personal lives of people, as also on their healthcare. In 2012, there were around 14.1 million cancer cases diagnosed worldwide, with 52.5% of those instances occurring in men and 47.5% in women. By 2030, that number is predicted to increase to 21.7 million. In 2012, this illness was responsible for 8.2 million fatalities worldwide. By the end of 2030, this figure is anticipated to increase to 13.0 million [1-3]. Most cancer-related fatalities take place in low- and middle-income nations, with little access to healthcare systems and medical resources [4]. Cancer patients are living longer because of the ongoing efforts to find a cure [5]. Initially, the Ehrlich tumor was identified in mice, as an unprovoked adenocarcinoma of the breast [6], exhibiting very aggressive activity, with the capacity to develop into a fast developing carcinoma, in practically all mouse strains [7]. The Ehrlich ascites tumor (EAT) model was one of the cancer models used to assess the anti-tumor properties of plant extracts [8-9]. In a female mouse, the EAT model first manifested as spontaneous breast adenocarcinoma. The mice were given subcutaneous transplants of tumor fragments, which developed into experimental tumors. Next, a different type of tumor was discovered developing in the peritonea of the mice, in the form of a liquid. Numerous investigations have used this model [10-11]. During the current study, we postulated that tumor preconditioning could have a far-reaching impact on the state of tissue oxidative stress.

When used alone or along with traditional anti-cancer medications, venom-based treatments, such as bee venom, show a promising potential in targeting the intrinsic vulnerabilities of glioblastoma tumors [12-13]. In a number of our earlier investigations, we have looked into the biological characteristics and proteome composition of venom. This venom possesses significant biological qualities that are relevant to pharmaceuticals, such as, anticoagulant, antibacterial, and anti-cancer effects [14-16]. Numerous bioactive compounds, such as the mast cell degranulating peptide (MCD-peptide), phospholipase A2 (PLA2), melittin, apamin, and hyaluronidase, have been verified by our proteome study. More often than

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not, melittin and PLA2, the two main components of the venom, have been shown to be responsible for the bioactivities mentioned above [17-18]. The venom's anti-cancer impact has frequently been seen on breast and colon cancers, but no research has investigated how it affects the glioblastoma [19]. Furthermore, because the microenvironment plays a crucial role in a cancer's mortality, these researches have been restricted to models *in vitro* and need additional confirmation *in vivo*. Thus, our goal in this study is to learn more about the possible anti-cancer effects the venom of A. mellifera syriaca has on glioblastoma, one of the most deadly cancers.

After testing its anti-cancer properties on glioblastoma cells *in vitro*, we created a mouse model that closely resembled an *in vivo* tumor, and analyzed the molecular mechanism by which the venom caused its toxicity. Our research investigated the therapeutic effectiveness of the A. mellifera syriaca venom and its capacity to tackle the intricate issues associated with the treatment of glioblastoma [20-21].

Materials and Methods

Induction of Tumors

We purchased Ehrlich Ascites Carcinoma (EAC)-carrying rats from the Biotechnology Research Center at Al-Nahrain University. Seven days after collection, sterile isotonic saline was used to suspend the Ehrlich Ascites Carcinoma (EAC) cells. Intrathoracic insertion of two and a half million viable EAC cells (Figure 1) into each animal was performed, to induce EAC, according to [2, 3, 22-24].

Animals

Forty Swiss albino mice, which were 20–25 g in weight, were purchased from an EVC animal house colony and kept for approximately 14 days in a room, with temperature ranging from 22°C to 25°C, under conditions of controlled relative humidity, with access to water and commercial food, and a 12-hour light/12-hour dark cycle.

Animal Groups

Four mouse groups (G1–G4) were randomly allocated

G1(A): Control; There was no medicine administered to the mice; G2(B): *Apis mellifera* (A.M); the mice received A.M orally (3.8 mg/kg bw/day) for 14 days according to [25]. G3(C): EAC; Around 2,500,000 EAC per mouse was administered intraperitoneally to the mice once [26]. G4(D): EAC + A.M; the mice in this group received an intraperitoneal inoculation of EAC, with around 2,500,000 EAC per mouse, followed by a 14-day oral treatment with CSE (3.8 mg/kg bw/day) on the second day.

Blood and Tissue Sampling

At the end of the sodium pentobarbital test, each animal received an intraperitoneal dosage of anesthesia (≥ 100 mg/kg). Whole blood samples and EAC fluid cells were removed from the peritoneal cavity of the mice and centrifuged for eight minutes, at 4,000 g. Before being subjected to a biochemical analysis, the serum was collected, and the kidneys, after removal of the samples, were cleaned with cold saline and fixed with 10% neutral buffer formalin. to conduct histological investigations. The samples were kept at -20°C.

Kidney Function and Electrolytes in the Serum

According to Patton and Crouch (1977), the sera from the mice had findings of urea and creatinine in them. The method suggested by [27, 28] was used, with pre-made devices that measured the levels of potassium, sodium, calcium, and chloride ions in the blood (Sensa Core Electrolyte, India).

Histopathological Investigations of the Kidney

For histopathological analysis, three kidney tissue samples from each mouse group were preserved in a solution of 10% formalin. The tissue slices were analyzed with eosin hematoxylin dye at 40× magnification [22, 26, 29-32].

Statistical Analysis

The mean ± SEM was used to express the data. The GraphPad Prism version 5 was used to analyze the mean differences in the group, by using a one-way ANOVA and a post hoc Tukey's test. If the p-value was less than 0.05, the mean difference was deemed to be significant.

Results

Impact of A.M. and/or EAC on the Body and Kidney Weights of Mice

Table 1 shows the changes in the groups of mice that had a large amount of fat around the kidneys. We noticed an increase in the weights of mice and a significant increase in the size of the kidneys after treating them with EAC, as compared to the control group. When the mice carrying EAC were treated with A.M, we noticed a decrease in the weight of the bodies and kidneys of these mice, when compared with the EAC group.

Effect of A.M on Kidney Function and Electrolyte Level

Table 2 we noted that EAC caused a significant increase in the levels of urea, creatinine, sodium, and chloride ions, and a significant decrease in the levels of sodium and calcium ions, when compared to the control group. When treated with EAC+A.M, we noted

Table 1. Impact of EAC and/or AM on the Body and Kidney Weights of Mice

	Control	A.M	EAC	EAC+ A.M
Mouse body weight (gm)	$24.54^{\#} \pm 1.33$	$22.24^{\#} \pm 1.04$	$35.62^{*} \pm 1.50$	$27.12^{\#*} \pm 1.55$
Mouse kidney weight (gm)	0.39 ± 0.03	0.35 ± 0.02	0.32 ± 0.05	0.33 ± 0.04

The mean ± standard error of ten observations is used to express the data. Significant differences of 0.05 between the control and EAC groups are shown by (*) and (#), respectively.

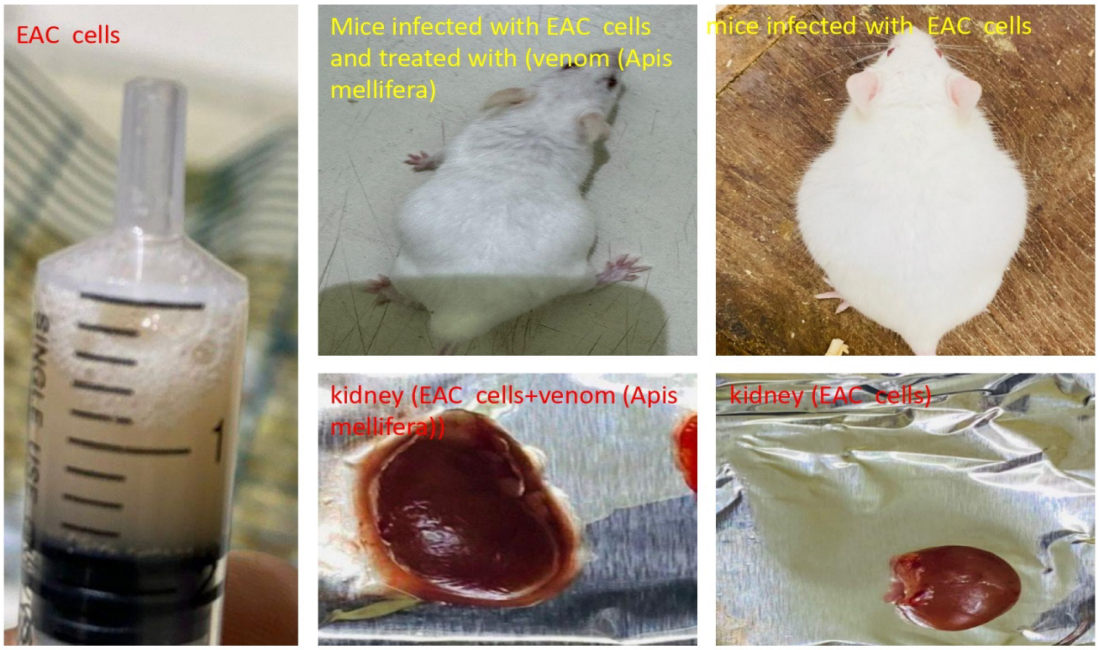

Figure 1. Legend?

Table 2. Alteration in Electrolytes and Renal Functioning in Several Populations

	Control	A.M	EAC	EAC+ A.M
Creatinine (mg/dl)	0.62#±0.03	0.50#±0.02	1.03* ±0.04	0.68#*0.02
Urea (mg/dl)	32.4#±2.66	33.4#±1.04	55.4*±1.60	36.6#±2.30
Na+(mmol/l)	134.3#±7.1	136.2#±8.4	129.5* ± 7.1	131.1#±6.2
K+(mmol/dl)	3.59#±0.21	3.71#±0.37	5.70*±0.19	4.05#*±0.22
Ca++ (mmol/dl)	1.30#±0.22	1.33#±0.11	0.80*±0.11	1.70#*± 0.22
Cl- (mmol/dl)	100.4#±7.1	105.4#±6.1	122.1*±10.2	111.2#* ±8.3

The mean ± S.E. of ten observations is used to express data. * and # indicate significant differences of 0.05 between the control and EAC groups, respectively.

a significant decrease in the levels of urea, creatinine, sodium, and chloride ions, and a significant increase in the levels of sodium and calcium ions, as compared to the EAC groups.

Kidney Histopathology

Changes in the histology and morphology of the kidney tissues in each treatment group and control group are displayed in Figure 2. The kidney sections of the

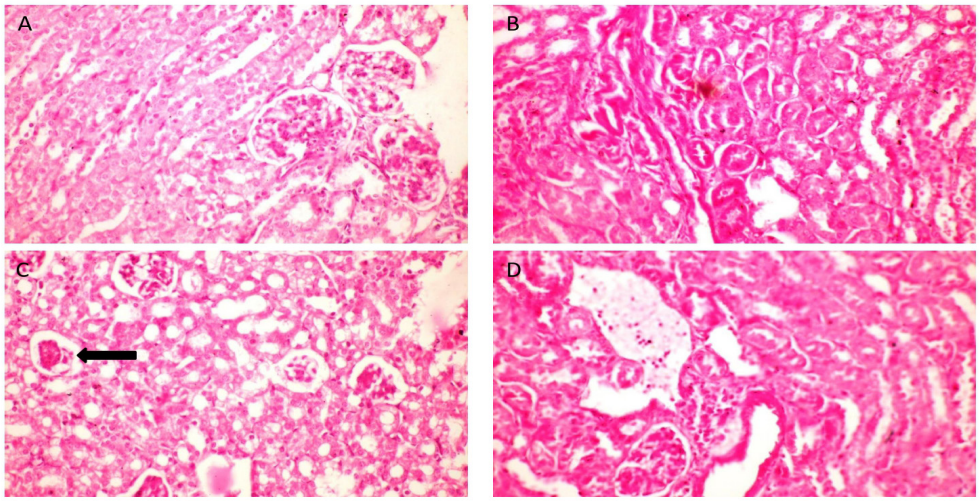

Figure 2. Legend?

control group had a normal histological structure; the two main kidney components, the medulla, and the renal cortex, both displayed the usual histological traits. The renal cortex was surrounded by a unique Bowman's capsule and glomerulus set in each of the several renal corpuscles. To make renal filtration easier, a normal, typical gap existed between the Bowman's capsule and the glomeruli. Convoluted tubules formed a network around the renal corpuscles (Figure 2A). The kidney parts — glomeruli and renal tubules — of the mice treated with A.M. showed the same normal structure as the control group (Figure 2B). In the kidney samples from mice infected with Ehrlich cells (EAC group), different pathological changes were seen in the glomeruli and renal tubules, including significant renal injury, considerable renal tissue degradation, noticeable cellular infiltration, and furthermore, the malpighian corpuscles had lost their characteristic form, as a result of the glomerular atrophy (Figure 2C). EAC was used to treat the kidney parts. When comparing the A.M. and the EAC groups, the histological structure of the kidneys showed a moderate degree of organization and improvement. The glomeruli showed remarkable improvement, whereas, the renal tubule atrophy showed considerable deterioration (Figure 2D).

Discussion

Cancer is believed to be the second leading cause of death worldwide, and while chemotherapy treatments are effective against many forms of cancer, they are limited by a number of adverse side effects and issues [33]. The Ehrlich ascites carcinoma initially appeared as an independent breast cancer with signs that resembled the more prevalent breast cancer [2]. There is proof that EAC cell invasion into the internal organs resulted in mitochondrial breakdown and inflammatory cell aggregation [34-35]. The Ehrlich ascites carcinoma lacked differentiation, developed rapidly, and responded well to therapy, making it similar to human malignancies [28]. As the ascetic fluid met the nutritional requirements of cancer cells, it was the direct source of sustenance for the progression of carcinoma.

Current tests for cytology in ascites fluid: Ascites fluid smears in EAC+A.M. showed a lot of apoptotic bodies and few EAC cells, but the tests indicated that the volume of the ascites fluid was increasing along with the cellular alterations, with a high number of EAC cells and a number of mitotic cells [3]. These findings concurred with those of [36]. They found that EAC-bearing mice had significantly higher abdomen circumferences, ultimate body weight, higher amounts of ascitic fluid, and a higher number of live tumor cells. These results aligned with those of [17, 37, 38]. They discovered that consuming seeds from the *Apis mellifera* (A.M.) plant caused weight loss in those with type 2 diabetes mellitus, who were overweight or obese. This study found that EAC caused renal dysfunction, which was manifested by increased reduced amounts of calcium ions (Ca++) and sodium ions (Na+), as well as urea, creatinine, potassium ions (K+), and chloride ions (Cl-). These changes in kidney functions and electrolyte levels may be related to EAC-induced renal tissue damage. These findings supported those of [39], who noted that the potassium, urea, and creatinine levels in mice rose following EAC induction. Additionally, recent findings agreed with those of [40, 41], who said that when kidney functions were elevated, EAC caused renal injury. According to recent findings, as compared to EAC alone, treatment with EAC with A.M. (EAC + A.M.) improved the previously evaluated renal functioning and electrolyte levels. These results were in line with those of [42-44]. They found that when the mice were given streptozotocin, black *Apis mellifera* (A.M.) enhanced renal functioning with the formation of Nε-CML. In a microscopic form, the kidney is a device resembling a tubular gland made up of a nephron and an intra-renal efferent urinary tract. Present-day histopathology: According to the findings, EAC damaged the kidneys, resulting in notable glomerular and tubular cell shrinkage and degeneration. According to the existence of renal damage in the group of mice that have EAC, the symptoms include kidney damage, as well as anomalies in the glomeruli and urine tubules in the kidney sections. These findings were consistent with those of [41-45], who revealed that EAC caused damage to the nephrons and urinary systems of female mice. These findings supported the findings of previous studies carried out by [46, 47], who showed that the alterations in kidney architecture and function might be due to the reactive oxygen species (ROS) that are produced by EAC. When under oxidative stress, which upsets cellular balance and results in tissue damage, ROS are essential.

Nevertheless, EAC treatments with A.M. demonstrated thicker glomerular basement membranes, better kidneys, with expanded glomeruli that enclosed the whole capsule, and a proximal tubule. Also, the structure in the glomeruli and renal tubules could be impacted by a number of hemodynamic and metabolic factors. These findings were consistent with the studies of both [48, 49].

In conclusion, the Ehrlich ascites carcinoma damaged renal tissues by reducing the sodium ion (Na+) and calcium ion (Ca++) levels, while raising the potassium ion (K+), creatinine, serum urea, and chloride ion (Cl-) activity. However, when treated with A.M., the EAC's impact on renal function and electrolytes was reduced, indicating that A.M. had a great ability to protect the kidneys.

Author Contribution Statement

Ahmed Flayyih Hasan, Mohanad Salam Hussein: They prepared the plan, designed the study, prepared the materials, photographed and performed the statistical analysis. Shahad Falah Abass, Ali G. Al-Dulimi, Hany M. El-Wahsh: They wrote, organized the images and references, and also helped answer reviewers' comments.

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Ethical Approval

The research protocol was granted approval by

the Ethics Committee of the Biotechnology Research Center,Al-Nahrain University.

Competing interests

The authors have no conflicts of interest or financial interests.

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