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RESEARCH ARTICLE

AMELIORATIVE EFFECT OF THE *AURELIA AURITA*CRUDE VENOM ON THE MURINE EHRLISH ASCITES CARCINOMA-INDUCED HEPATOTOXICITY AND NEPHROTOXICITY.

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Abstract

The ability of Jellyfish, *Aurelia aurita*(*A.A*)crude venom to modify the hepatic and renal dysfunction associated with Ehrlish ascites carcinoma (EAC) stress in experimental mice was assessed. Intraperitoneal injection of *A.A.* crude venom into EAC-bearing mice at different doses (50, 125, 250, 500,750 mg/kg B.W), daily, for 7 days was compared with the standard drug, cisplatin, (2mg/kg). Loading the mice with EAC significantly reduced the red blood cells counts and subsequently reduced the hemoglobin (HB). Administration of *A.A* venom significantly restored red blood count and HB. EAC load had increased the activities of serum AST and ALT but decreased the concentration of albumin and total protein.
A.A. crude venom as well as cisplatinimproved the hepatic injury by declining the ALT activity and increasing albumin values but no significant changes in the total protein were observed. Moreover, levels of the renal biomarkers, creatinine and urea were highly elevated in EAC-bearing mice. Interestingly unlike cisplatin, levels of those renal biomarkers, creatinine and urea, were significantly decreased by *A.A.* crude venom administration. Furthermore, histopathological examinations revealed hepatic and renal tissues improvement in EAC-loaded mice after venom administration compared with control group. Taken together, results from thisstudy suggest that *A.A* crude venom can potentially reduce the hepatic and renal damage induced by EAC load in experimental animals.

Introduction:-

Marine environment has always been considered as rich sources of both biological and chemical diversity. Marine organisms are the main sources of structurally diverse bioactive compounds. The great deal of interest has been expressed regarding marine derived bioactive peptides because of their numerous health related beneficial effects **(Kim and Wijesekara, 2010).**

Cnidarians venoms have roles in drug discovery as the toxic compounds isolated from cnidarian have been viewed to produce several serious implications to human health due to their neurotoxicity, cytotoxicity and tissue damage. Their toxins might offer a tool to study cell physiology **(Morabito*et al.*, 2015)** and provide promising sources of pharmacological agents for therapy of human diseases.

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Biological properties of venom from terrestrial animals have been extensively investigated, while scarce research has been undertaken jellyfish venom. Most of the proteinaceous venoms showing marked curative properties are from highly toxic species (snake, scorpion, etc) and their high toxicity hinders clinical trials. Hence, less toxic species like jellyfish represent a valuable source of pharmacological compounds that may lead compounds for new drugs.

In vitro toxic action of the venom from *A.A*has received some attention. Lethality and dermonecrosis were observed in mice, with variouspotencies depending on the origin of the specimen **(Radwan*et al.*, 2001)**. The venom is hemolytic to human, sheep, and bovine red blood cells **(Radwan*et al.*, 2001, Segura *et al.*, 2002** and **Rastogi*et al.*, 2012)**. Protease and phospholipase A activities were recorded to change in response to such venom **(Nevalainen*et al.*, 2004**and **Lee *et al.*, 2011)**.

Previous studies concluded that SDS-PAGE electrophoresis revealed that the crude venom of *A.A* contains several bands between 200 and 6 kDa**(Rastogi*et al.*, 2012)**. The venom was purified by chromatography and the neurotoxic activity of some fractions was characterized. The protein fractions named Aa-1 and Aa-2 were identified and used for further studies. After intramuscular injections with 0.06 mg protein/kg in 0.1 ml/vol of fractions Aa-1 or Aa-2, adult crabs developed tetanic reactions followed by total paralysis and death within three minutes. The molecular weights of Aa-1 and Aa-2 were 66 and 45 kDa, respectively **(Segura *et al.*, 2002** and **Ponce *et al.*, 2013)**.

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body and associated with different organs disorder. Cisplatin has become one of the most used drugs in the treatment of solid tumors of epithelial origin. Although cisplatin has been a mainstay for testicular cancer therapy **(Einhorn, 1997**), it is also commonly used to treat ovarian, cervical, bladder, and non-small cell lung carcinoma as well as head and neck cancers **(Armstrong, 2006, Helm and States, 2009** and **Konstantakou, 2009)**. The two limiting factors for a successful application of cisplatin are acquired or intrinsic drug resistance of the tumor and severe side effects in normal tissues, mainly in the kidney, in the inner ear and in the peripheral nerves **(Pabla and Dong, 2008**).

In this regard, the present study aimed to evaluate the potency of *A.A*crude venom to improve the hematological, biochemical and histological injuries induced in the kidney and liver byEAC-loaded in the experimental mice and compare this effect, if there is any with this of cisplatin as one of anticancer drug.

Material and Methods:-

A.A sampling areas:-

*A.A*was collected during June, 2014 from the Red sea "Wadi el Gemal protected national park" from North head Hnkurab and North head Baghdadi areas.

Venom preparation:-

*A.A*crude venom was prepared as described by **Torres and Heimer, (2001)** as follows; the oral arms and tentacles of organisms were clipped manually, combined and centrifuged at 1620 g for10 min at (4ºC). The pellet was resuspended in distilled water, lyophilized and stored at (-20ºC). The nematocysts rupture was monitored optically in order to obtain their maximal discharge. The best technique for nematocysts discharge was obtained by applying an osmotic shock by resuspending freshly lyophilized samples in deionized water (1mg/10µl), this preparation was stirred for two minutes and centrifuged at 1932 g for 30 min at (4ºC). The supernatant was then centrifuged at 11130 g for 20 min at (4ºC), and filtered (0.45µm). The venom isolated and resuspended in this form, maintained full activity when stored at (-20ºC) for 1 month.

Expermintal animals:-

One hundred twenty *Swiss albino* female mice were purchased from Faculty of Pharmacy Mansoura University. They were housed in plastic cages under standard condition of humidity, temperature, chow and water in the animal lab of Faculty of Science, Port Said University until became of suitable weight. EAC-bearing albino mice (tumor donor animals) were obtained from Tumor National institute, Cairo, Egypt. These mice were kept in the same conditions of normal mice.

1 ml Ehrlish tumor cells were drawn and diluted with saline (0.9% NaCl). Using haemocytometer, the tumer cells were counted and 0.2 (1×10^7) ml of freshly drawn diluted ascites fluid were intraperitonealy injected into the normal experimental mice.

Experimental design:-

Animal grouping:-

After 72h of Ehrlish tumor cell injection, Female mice were grouped as follows

1. **Group1. Normal mice (Normal control)**
   a. Normal mice were I.P injected with 0.9% normal saline.
2. **Group2. EAC-bearing mice (Positive control)**
   a. Normal mice were I.P injected with 0.2 ml (1×10^7) tumor cells/mouse.
3. **Group3. EAC+ (50 mg/kg BW)**
4. **Group4. EAC+ (125 mg/kg BW)**
5. **Group5. EAC+ (250 mg/kg BW)**
6. **Group6. EAC+ (500 mg/kg BW)**
7. **Group7. EAC+ (750 mg/kg BW)**

_A.A_ crude venom daily for 7 days

8. **Group8. EAC+cisplatin:**Tumor-bearing mice after 72 h of tumor cell injection were I.P injected with the standard drug at dose (2mg/kg) every day for 7 days as standard drug control **(El-Nagar, 2011).**

Collection of samples:-

The bloodsamples were collected from control group and treated groups after 7 days of daily treatment. Blood samples were collected in EDTA tubes for hematological analysis, another blood sample were left for clotting, centrifuged at 300 rpm for 15 minutes and immediately frozen at (-20ºc) till the biochemical assay (ALT, AST, albumin, total protein, urea andcreatinine) were carried out. Kidney and liver of the normal, EAC-bearing albino mice and treated animals were fixed in formalin (10%) for histopathological assay.

Hematological and Biochemical assays:-

Complete blood count (CBC) includes hemoglobin content, Red blood cells (RBC), white blood cells (WBC), and platelets (PT) counts. It was done by Abbott CELL-DYN1800 automated hematology analyzer, USA, using ready–made kits produced by Abbott laboratories, Abbott Park, IL, 60064, USA. Serum biochemical analysis was determined by colorimetric methods using ready-made kits produced by Linear Chemicals. S.L. Biochemical, BIOMED, SPINERACT diagnostic assays include Aspartate transaminase (AST), Alanine transaminase (ALT), Albumin, Total protein, Urea and Creatinine.

Statistical analysis:-

Data was statistically analyzed using Minitab, using a MINITAB (Lenth, 1989). Tabulation and graphics of data were done using Microsoft Excel XP. All of the data of control and treated groups were expressed as mean values ± standard error. One-way ANOVA and unpaired t-test were carried out to find if there was any significant difference among control and treated groups with *A.A* crude venom at different doses.

Results:-

Haematological assay:-

The alteration of hematological parameters induced in EAC-bearing albino mice and the protective effect of *A.A* crude venom are given in **table (1)** comparing to cisplatin post treatment.

As shown in Table (1) EAC-bearing albino mice had a significant decline in Hb, Red blood cells but non-significant changeof White blood cell, and platelet counts when compared with control group. Administration of different doses of *A.A* crude venom after injection with EAC had significantly increased Hb, Red blood cell. While non-significant changes were observed on the Hb levels in the groups administered with doses 125, 250, 500 and 750 mg/kg BW of *A.A*crude venom. Adminstration of the standard drug, cisplatin, at dose of 2mg/kg, showed non-significant changes in hemoglobin levels and significant elevatation in the RBCscount when compared with the EAC control group.

Table 1:- Effect of *A.A*crude venom and(2mg/Kg BW) Cisplatinon hematological parameters of EAC-bearing *Swiss albino* female mice.

Parameter / Groups	Haemoglobin (g/dL)	RBCs count ($\times10^6$/µL)	WBCs count ($\times10^3$/µL)	Platelets count ($\times10^3$/µL)
Normal control	9.58±0.258	5.212±0.104	8.02±0.229	194.4±17.608
EAC control	7.26±0.597 ^{b**}	2.8±0.10 ^{b***}	6.5±0.776	115.8±1.907
EAC + Cisplatin (2mg/Kg BW)	6.98±0.427	2.24±0.051 ^{a***}	8.06±0.112	97.2±2.956 ^{a***}
EAC+50mg/kg *A.A* venom	9.18±0.262 ^{a*}	5.08±0.454 ^{a***}	7.86±0.384	118±4.898
EAC+125mg/kg *A.A* venom	8.5±0.519	4.854±0.613 ^{a**}	9.62±0.220 ^{a**}	150.2±3.942 ^{a***}
EAC+250mg/kg *A.A* venom	8.34±0.627	5.03±0.638 ^{a**}	10.04±0.549 ^{a**}	170.4±17.823 ^{a**}
EAC+500mg/kg *A.A* venom	9.08±0.600	5.09±0.286 ^{a***}	9.78±0.950 ^{a*}	174.2±20.582 ^{a*}
EAC+750mg/kg *A.A* venom	8.58±0.888	4.97±0.595 ^{a**}	8.52±1.047	194.8±10.767 ^{a***}
ANOVA(Pvalue)	_	0.000	0.005	0.000

Results expressed as Mean± SE (n=5). ANOVA (P value) represents the difference between all groups. ^{a}represents significantly different comparing with EAC control group. ^{b} represents significantly different comparing with normal control group.*($p<0.05$),**($p<0.01$),***($p<0.001$).

Biochemical Assay:-

a-Hepatic biomarkers:-

The changes in the serum liver biomarkers are shown represented in Figure 1(A, B. C, D).

EAC load in albino mice induced hepatotoxicity which is represented as significant increase in liver biomarkers; serum AST and ALT activities ($P \leq 0.01$& $P \leq 0.05$) respectively. Both treatments with different doses of *A.A*crude venom at all doses 50, 125, 250, 500 and 750 mg/kg BW and the standard drug, cisplatin, non-significantly changed AST activities while different doses of *A.A*crude venom at all doses 50, 125, 250, 500 and 750 mg/kg BW and the standard drug, cisplatin, significantly declined ALT activities and ameliorate the hepatotoxicity induced by EAC as noticed in Fig 1-A and B

Moreover, Serum albumin, total protein were highly significant decreased ($P \leq 0.001$) in EAC-bearing *albino* mice. I.P treatment of EACs-bearing mice with *A.A* crude venom induced significant increase ($P\leq 0.05$) in albumin levels at dose 50, 125 and 250 mg/kg BW and non-significant changes at higher doses 500 and 750 mg/kg. Similarly, the standard drug, cisplatin, induced a very highly significant increase ($P\leq 0.001$; Fig 1C)

I.P treatment of EACs-bearing mice with different doses of *A.A* crudevenom induced non-significant changes in the serum total protein content at low doses 50, 125 and 250 mg/kg BW. Meanwhile, high doses 500 and 750 mg/kg BW of *A.A* crudevenom caused very highly significant decrease ($P \leq 0.001$ and $P \leq 0.01$). Treating EAC-control mice with the standard drug, cisplatin, induced non-significant changes as shown in**fig1D**.

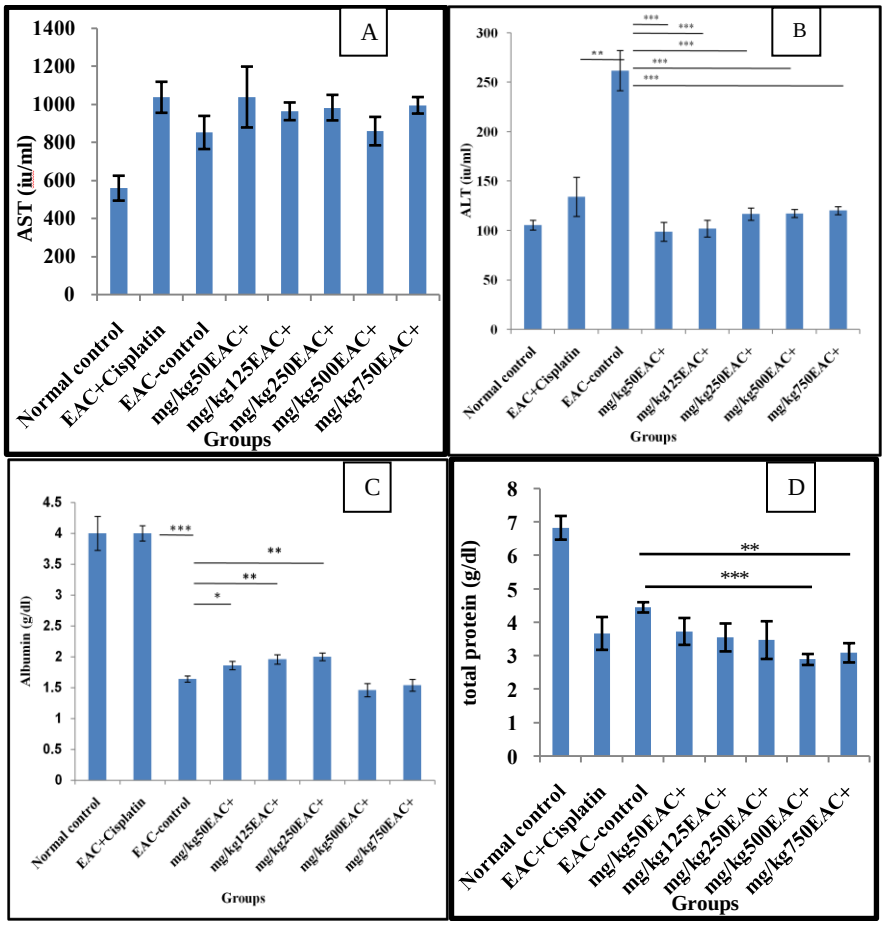

Figure 1:- Effect of A.A crude venom on the alteration of biochemical markers induced by EACs-bearing mice, (A) AST, (B) ALT, (C) albumin and (D) total protein levels. * ($p<0.05$),** ($p<0.01$), ***($p<0.001$).

Renal Biomarkers:-

EAC-bearing albino mice induced renal damage which is represented as disturbance in renal biomarkers (creatinine and urea). As shown in Fig 2, urea had non-significantly changed ($P \leq 0.001$), while creatinine was significantly increased in EAC-bearing albino compared to those of the normal mice.

Treatment of EACs-bearing mice with different doses of *A.A.* crude venom caused a significant decline in serum urea and creatinine at all doses 50, 125, 250, 500 and 750 mg/kg BW respectively. On the other hand, EAC-control mice treatment with cisplatin did not induce any noticeable changes in urea concentration but caused a significant increase ($P \leq 0.01$) in creatinine, as illustrated in **figure 2A,B.**

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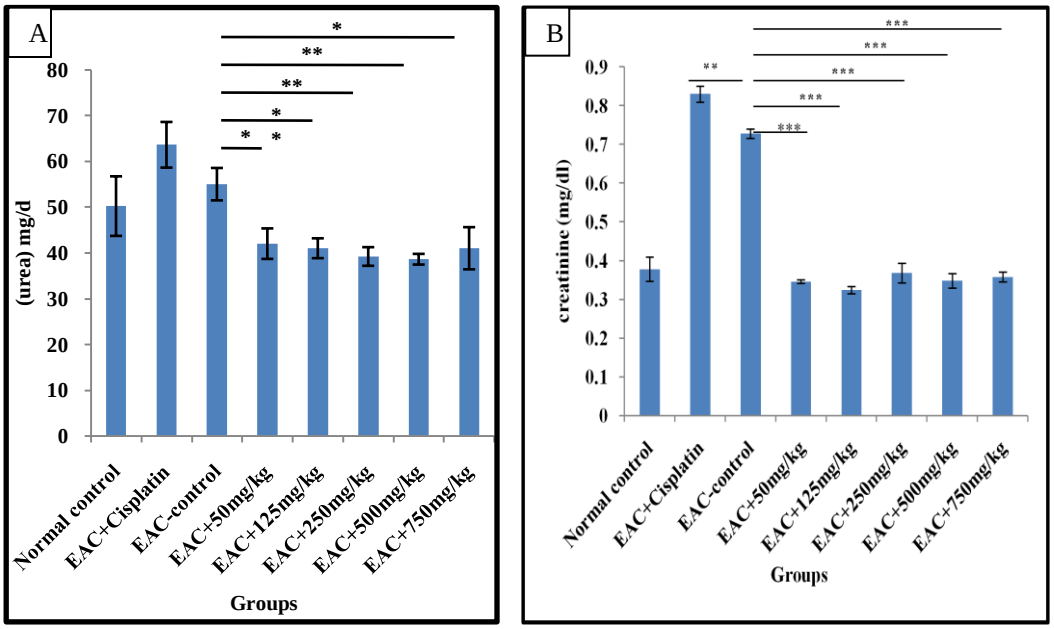

Figure 2:- Effect of A.A crude venom on the alteration of biochemical markers induced by EACs-bearing mice. urea (A), creatinine (B), * ($p<0.05$), ** ($p<0.01$), *** ($p<0.001$).

HistopathologicalAssay:-

Liver and kidney from EAC-loaded mice, *A.A* crude venom-treated EAC-bearing mice and cisplatin treated EAC-bearing mice were represented in Fig 2 and 4. As shown loading mice by EAC deteriorate lobular architecture where hepatocytes showed enlarged nuclei, hydropic degeneration and sinusoidal infiltration of carcinoma cells mixed with lymphocytes**.** In addition**,** marked degenerative changes of renal tubules, stromal congestion and moderate inflammation with mild degeneration of glomeruli, an improvement in hepatic and renal tissues in EAC-loaded mice after *A.A* crude venom administration was observed at **figures 3 (A-H)**.

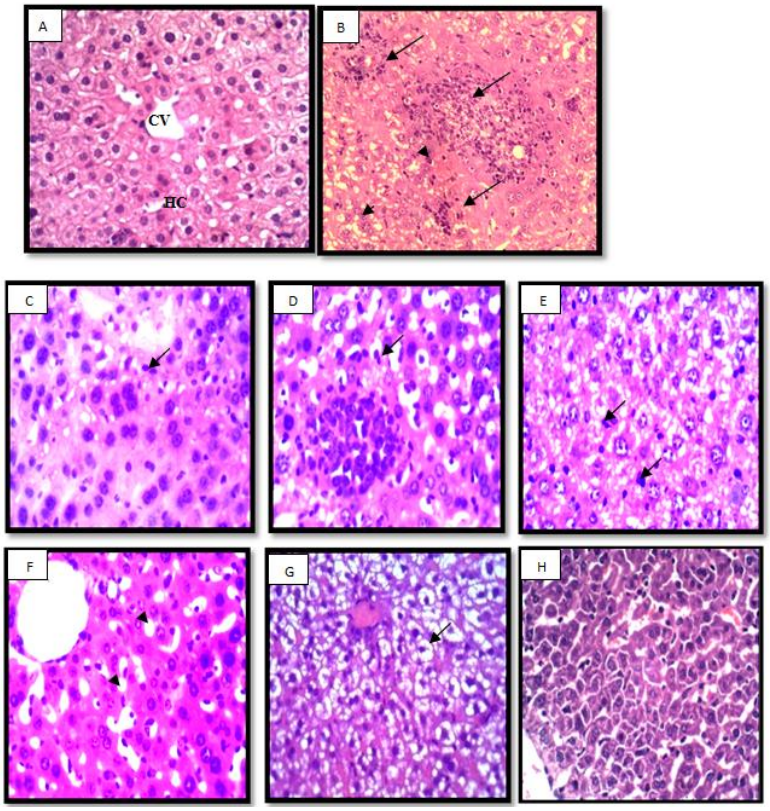

Figure 3:- Histopathology of liver in normal and EAC-bearing mice groups. **A-** Section of liver of normal control mice showing normal histological appearance of liver including central vein (CV), hepatic cells (HC). **B-** Section of liver of EAC-bearing mice illustrating hydropic degeneration (arrow head) and sinusoidal infiltration of carcinoma cells mixed with lymphocytes (arrows). **C-** Section of liver of **50** mg/kg BW *A.A.* venom-treated EAC-bearing mice showing shrunken deeply stained nuclei (arrow). **D-** Section of liver of **125** mg/kg BW *A. A.* venom-treated EAC-bearing mice showing shrunken deeply stained nuclei (arrow) **E-** Section of liver of **250** mg/kg BW *A.A.* venom-treated EAC-bearing mice showing restored normal lobular architecture, still to notice very few hepatocytes showed shrunken deeply stained nuclei (arrow). **F-** Section of liver of **500** mg/kg BW *A.A.* venom-treated EAC-bearing mice showing mild improvement with hydropic degenerative changes (arrow head). **G-** Section of liver of **750** mg/kg BW *A.A.* venom-treated EAC-bearing mice showing: marked improvement with mild degenerative changes (arrow). **H-** Section of liver of 2mg/kg BW **cisplatin**-treated EAC-bearing mice illustrating some hepatocytes hydropic degeneration and ballooning degeneration (arrow head). Slides captured with Power Field of 400x

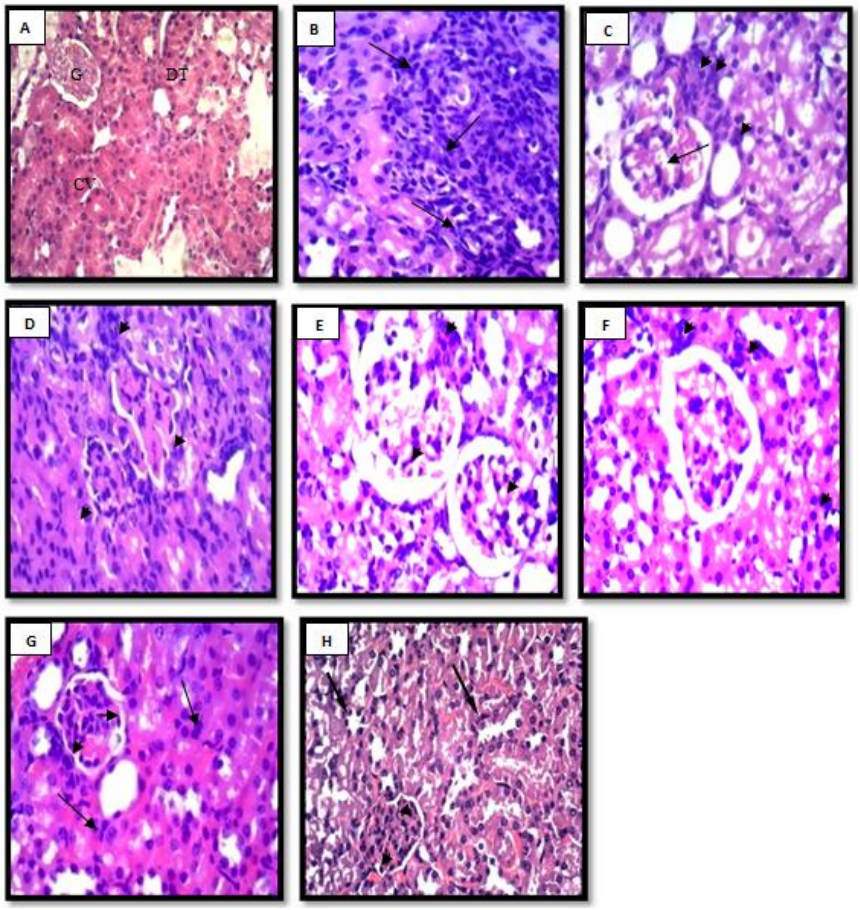

Figure 4:- Histopathology of kidney in normal, EAC-bearing and treated EAC-bearing mice groups. **A-** section of the cortical tissue of the kidney of control normal mice showing glomeruli(G), proximal and distal convoluted tubules (DT) **B-** Section of mice kidney of EAC–control group showing moderate inflammation with mild degeneration of glomeruli, accompany the infiltration of many proliferating groups of neoplastic cells (arrow). **C-** Section of mice kidney of **50** mg/kg BW *A.A.* venom-treated EAC-bearing mice. **D-** Section of mice kidney of **125** mg/kg BW *A.A.* venom-treated EAC-bearing mice illustrating degenerative changes of tubules and inflammation with mild degeneration of glomeruli (arrow) Neoplastic cells are fewer than EAC control denoting minimal improvement (arrow head) **E-** Section of mice kidney of **250** mg/kg BW *A.A.* venom-treated EAC-bearing mice showing cortical tissue few of neoplastic proliferation with minimal glomerular capillary congestion (arrow head). **F-** Section of mice kidney of **500** mg/kg BW *A.A.* venom-treated EAC-bearing mice showing fewer neoplastic cells are than EAC control denoting minimal improvement (arrow head). **G-** Section of kidney of **750** mg/kg BW *A.A.* venom-treated EAC-bearing mice showing kidney totally free of neoplastic proliferation with minimal glomerular capillary congestion (arrow head) and mildly degenerated tubules (arrow). **H-** Section of kidney of 2 mg/kg BW cisplatin-treated EAC-bearing mice showing degeneration of tubes and congestion of corpuscles (arrowhead) and mildly degenerated tubules (arrow). Slides captured with high Power Field (HPF) of 400x.

Discussion:-

Several marine organisms are of considerable interest as a new promising antitumor source. The present investigation showed the ability of *A.A* crude venom at different doses 50, 125, 250, 500 and 750 mg/kg BW to restore the hematological, biochemical, histopathological disorders developed in experimental mice bearing EAC cells.

The current study revealed that anemia is associated with loading the mice with EAC. It was reported that anemia encountered in tumor bearing mice is mainly due to reduction in RBC and/or hemoglobin percentage and this may occur either due to iron deficiency or due to hemolytic or myelopathic conditions **(Fenninger and Mider, 1954** and **Sinclair, *et al.*, 1990).**

In the current study, hemoglobin content, RBCs count and platelets count showed significant decrease in EAC-bearing control mice. Interestingly, treatment with *A.A* crudevenom with different doses induced appreciated increase in hemoglobin, RBC, WBCs and platelets counts after venom injection. The increase in RBCS, hemoglobin and platelets after treated with *A.A* crudevenom are running in agreement with the data by **Zaki, (2005)** who proved the antitumor effect of sea cucumber, *Holothuriaatra,* crude venom on biochemical and hematological parameters on rat, and suggested that this increase in the in RBCS, hemoglobin and platelets may be attributed to activation of the bone marrow by sea cucumber. Similarly, this explanation runs in agreement with **Jakowska*et al*., (1958)** who reported that the toxin of sea cucumber stimulates hemopoiesis in the bone marrow.

The increase in hemoglobin levels, RBCs, WBCs and platelets counts indicates that *A.A* crude venom may possesses a protective action for the hematopoietic system. On the other hand, the significant increase in WBC's may result from the stress induced by venom injection as reported by **Bawaskar, (2012)** who studied the effect of scorpion sting.

The fact that haemoglobin and RBC content are increased in *A.A* crude venom-treated groups is consistent with the result by **Meenakshi*, et al*., (2013)** and this result by **Abd El-Aziz *et al*., (2014)** who studied the inhibitory effects of Rosemary (*Rosmarinusofficinalis L.*) on EAC-bearing mice. Similar effect was observed by **Gupta *et al*., (2004)** for the extract of *Bauhinia racemosa* stem bark on EAC bearing mice. Moreover the increase in platelets count might be due to platelets activation according to **Konca *et al*., (2014)** who reported that during his study on the platelet function in children with scorpion envenomation.

In cancer chemotherapy, the major problems are myelo suppression and anemia **(Price and Greenfield, 1954)**. In the present study, the treatment of EAC-bearing mice with the standard drug, cisplatin induced significant decrease in RBCs, hemoglobin and platelets levels comparing with EAC-control mice. Based on these results, *A.A*crude venom may has an advantage to restore the haematological parameters which distorted by cancer in EAC-bearing mice model.

Hepatic enzymes including ALT and AST showed a significant elevation in the EAC control group in comparison with normal control which indicates the hepatocellular damages caused by inoculation with EACs **(El-Dayem*et al*., 2013).** Moreover, our results revealed that the levels of hepatic enzymes (ALT, AST) were elevated in the EAC-bearing mice. Administration of *A.A* crude venom to EAC-bearing mice reduced the elevated ALT level indicating a recovery from EAC hepatotoxicity. Reduced level of this hepatic enzyme in serum is one of the indications of the antitumour potential **(Chakraborty*et al*., 2006** and**Sundaram*et al*., 2012).**

The current study demonstrated that the treated mice with different doses of *A.A* crude venom can elevate the plasma level of AST; this might be due to hepatocellular toxicity. Treatment with cisplatin as a standard drug elevated transaminases values indicating a hepatic toxicity too.

In support of this finding, elevation in the plasma levels of AST also agrees with the data by **Liang *et al* (2011)** who studied the effects of tentacle-only extract from the jellyfish *Cyaneacapillata*sp and the results by **Bruschetta *et al*., (2014)** who studied the inflammation and oxidative stress by the crude venom extracted from the jellyfish *Pelagianoctiluca* in rats.

Abu-Amra*et al*. (2015) studied the role of bradykinin potentiating factor (BPF7) separated from jellyfish, *Cassiopiaandromeda*. It was suggested that the marked increase in this hepatic enzyme by this factor may be due to an enhancement of protein biosynthesis, changes of cellular permeability and release of cyclic AMP. This suggestion was also recommended by **Enjalbert*et al*., (1980), Etgen and Browning, (1983), Abu-Amra and Abd El-Rehim, (1992)** and **Abu-Amra (2000).**

On the other hand, the biochemical results of EAC-bearing mice revealed a decrease in the albumin and total protein levels; this may be attributed to increased mitotic division of tumor cells with high body fluid withdrawal and the capillary permeability, which permit the escape of plasma proteins into peritoneal cavity **(Garrison *et al*., 1987).**

Furthermore, hypoproteinemia and hypoalbuminemia may be due to excessive nephritis and/or massive ascites and also associated with liver disease. This is in parallel to increased AST activity which may be attributed to hepatic damage as a result of cancer cells invasion **(Badr*et al*., 2011)**. Treatment of EAC-bearing

mice with *A.A* crude venom had significantly increased albumin level in a dose-dependent pattern in lower doses (50, 125 and 250 mg/kg BW) and return to decrease albumin level non-significantly in the higher doses (500 and 750 mg/kg BW), while treatment with cisplatin elevated albumin value to be restored to normal values.

This change of albumin levels recorded in the *A.A* crude venom-treated animals is in agreement with **Abd El-Aziz *et al*., (2014)**. The decrease in albumin level in Ehrlich group and its improvement by *A.A* crude venom may be due to *A.A*hepatoprotective activity in EAC-bearing-treated mice. In line with these findings, **Natesan*et al*., (2007)** and **Senthilkumar*et al*., (2008)** showed that the methanol extract of *Careyaarborea* (has antitumor effect) have a hepatoprotective activity in EAC-bearing mice.

In the present study we found a decrease in total protein level after the administration of *A.A* crude venom. The same effect was observed in the cisplatin-treated EAC-bearing mice. This decrease in total protein level after the administration of *A.A* crude venom agrees with the study by **Zaki, *et al*., (2005)**. This decrease may be due to increased catabolism of plasma proteins, or to impaired synthesis of the protein.

It was demonstrated that, the presence of tumors in human body or experimental animals is known to affect many functions of vital organs **(DeWys, 1982)**. At the current study, urea and creatinine levels, which are considered as makers of kidney function, were significantly elevated in serum of EAC-control mice indicating renal impairment. These alterations induced by toxic conditions, reflected metabolic cellular dysfunction of these tissues **(Robbins *et al*., 2001)**. An elevation of urea may be attributed to an increase in nitrogen retention or excessive protein breakdown **(Geraci*et al*., 1990).**

Treatment with *A.A* crude venom gradually returned the increased levels of urea and creatinine to more or less the normal values, while the treatment of EAC-bearing mice with cisplatin maintained their higher values.

Histopathological assay offered more evidence for improving the EAC-induced cytotoxicity by *A.A* crude venom. Treatment with different doses of *A.A* crude venom especially high doses showed regular hepatocytes with abundant cytoplasm with mild hydropic degeneration and mild degenerative changes similar to control.

In addition, treating EAC-bearing mice with the *A.A* crude venom especially, at the highest doses shows kidney totally free of neoplastic proliferation with minimal glomerular capillary congestion and mildly degenerated tubules with interstitial inflammation. This result is similar to that reported by **Nagarjuna*et al*., (2013)** when they studied the anti-cancer activity of *Ruelliatuberosa* on EAC induced mammary tumor.

In conclusion, loading mice with EAC-bearing mic- induced haematological, hepatic and renal toxicity. I.P administration of *A.A* crude venom could restore the hepatic and renal biomarkers which were disturbed by EAC application, moreover, *A.A* crude venom had improved the histopathological disturbances by EAC load. This biological activities induced by *A.A* crude venom might be attributed to some bio-active compounds. Further researches are still required to separate and identify the biologically active protein of *A.A* crude venom individually, then determined the biological mechanism of the effective fraction/s.

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