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The Marine Alga *Enteromorpha compressa* as a Green Modulator of Systemic Alterations: Insights from an Induced Tumor Mouse Model

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ABSTRACT

Marine ecosystems are recognized as an incredible source of natural products that demonstrate notable pharmacological activities. The marine macroalga *Enteromorpha compressa* is an edible alga which is widely distributed along the Mediterranean Sea. Therefore, this study aimed to evaluate the impact of ethanolic and aqueous extracts of *E. compressa* collected from the Mediterranean Sea coast, Port Said, Egypt in cancer induced mouse model. Ehrlich ascites tumor cells were inoculated intramuscularly in the thigh muscle of mice, then tumor induced mice were treated with low and high doses (100 and 200mg/ kg) of both ethanolic and aqueous extracts of *E. compressa*. Aqueous extract showed higher amounts of phenols and flavonoids (10.5 ± 0.45 µg gallic acid equivalents per gram of extract, 7.9 ± 0.4 µg rutin equivalents per gram of extract, respectively) than ethanolic extract (7.9 ± 0.34µg GA E/mg and 5.9 ± 0.3 µg R E/mg, respectively). Antioxidant property of the extracts was confirmed by the significant increase (P<0.05) in the total antioxidant capacity of treated mice. Significant decreases in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, and urea were observed (P<0.05) in all extract treated groups compared with the untreated Ehrlich solid tumor (EST) control group. Moreover, histological examination of tumor, liver, and kidney tissues revealed that *E. compressa* extracts possessed ameliorative effects on these organs alterations. The treatment with high and low doses of aqueous extract revealed marked improvement in treated mice, superior to ethanolic extract. Furthermore, *E. compressa* extracts possessed a marked enhancement effect on hematological parameters by modulating the count of white blood cells, platelets, red blood cells, and hemoglobin concentrations among the treated groups. Finally, *E. compressa*, as a marine organism, is a valuable source for discovering the field of eco-friendly green sources for treatments of many health disorders via further recommended studies.

INTRODUCTION

Cancer is one of the most worldwide prevalent fatal diseases in the world. In 2020, according to the World Health Organization (WHO), about 10 million people died from cancer. Hence, it is considered the second leading cause of mortality. In addition, over 35 million of new cancer cases are expected in 2050. Unfortunately, different strategies used for cancer treatment are a double-edged sword because of their non-selective cytotoxicity **(Behranvand *et al.*, 2021)**. Cancer cells are characterized by uncontrolled growth,

resistance to apoptosis, and their ability to invade the surrounding tissues in a process known as metastasis. Metastatic tumor growth threatens the lives of cancer patients as tumor cells spread out of control the signals that regulate cell proliferation. Thus, many attempts have been made to develop alternative approaches that enhance treatment effectiveness while minimizing the impact on healthy cells. Consequently, scientists redirected their efforts toward using natural products for developing more effective anticancer drugs with minimal adverse effects, due to their biological activities compared with traditional therapies **(Chunarkar-Patil *et al*., 2024)**. It is estimated that more than 60% of commercially therapeutic drugs are derived from natural sources **(Patridge *et al*., 2016)**.

The Ehrlich tumor originates from mammary adenocarcinoma in mice and develops into an ascites through serial passages in the peritoneal cavity. Ehrlich carcinoma (EC) in both ascitic and solid forms remains a valuable tool that is widely used in cancer research. Therefore, it is used to explore tumor growth, immune system interactions, and physiological processes, as well as investigating novel diagnostic strategies and therapeutic drugs outcomes. Ehrlich cells have capability to induce a high-rate of malignant cells proliferation, accurately predicts survival duration and analogous to abnormal physiological changes and behavioral patterns in human **(Feitosa *et al*., 2021)**.

Marine-based resources are considered as ultimate source of bioactive compounds owing to their significant levels of biodiversity **(Rigogliuso *et al*., 2023)**. Marine organisms as algae, corals and crustaceans are exposed to various extreme conditions as predators and environmental factors. Thus, these organisms yield promising bioactive secondary metabolites as a defense mechanism. Marine-derived secondary metabolites exhibited a wide range of potent biological activities such as anticancer, antimicrobial, antifungal, antiviral and immunomodulatory activities **(Al-Hussaniy *et al*., 2025)**.

Algae are photosynthetic organisms that grow in various habitats such as lakes, rivers, and oceans. They are generally categorized into macroalgae (seaweed) and microalgae (unicellular) based on their photosynthetic pigments which absorb light with different wavelengths accordingly give them their attractive unique colors. Groups of algae are divided into rhodophyta (red algae), phaeophyta (brown algae), and chlorophyta (green algae). The marine algae are consumed as a high-value food source for human and animals **(Matos *et al*., 2022)**. They are also valuable resources of minerals, iron, potassium, phosphorus, vitamins, and pigments **(Arora and Philippidis, 2023)**. Algae are exposed to severe environmental conditions fluctuations in temperature, pH, sunlight, and carbon dioxide supply. While adapting to new environmental surroundings alterations, they produce a wide variety of secondary bioactive compounds as peptides, sterols, quinones, glycerol, polysaccharides, alkaloids, fatty acids, phenolic compounds, pigments, and terpenoids. It is reasonable to suppose that secondary metabolites produced by marine organisms differ greatly from other terrestrial species due to the significant variations in their environment. According to recent research, these metabolites exhibit a

panel of interesting biological activities such as anticancer, anti-inflammatory, antioxidant, antiviral, antimicrobial and antidiabetic properties **(Gazali *et al*., 2021; Kumar *et al*., 2025)**. In recent years, researches on new bioactive molecules that possess potential medicinal or other commercial uses have shed light on discovering the chemistry of marine algae **(Pereira and Valado, 2023)**.

Enteromorpha compressa is an edible green algal species that belongs to the Ulvaceae family that is broadly distributed along the Mediterranean Sea, North America and throughout Africa and Australia. Moreover, its biological activities as anticancer, anti-allergic, antiviral, and antioxidant agents **(Pradhan *et al*., 2020)**, additional reports have suggested that different extracts of *Enteromorpha* genus possess an anticancer activity in cancer induced animal model **(Das *et al*., 2021)**. Alcoholic and aqueous extracts of chlorophyta displayed *in vivo* and *in vitro* anticancer activity against different cancer types, since the variable conditions may influence the diversity of their bioactive phytoconstituents **(El Moudden *et al*., 2022)**. This study aimed to evaluate the potential anticancer and the systemic ameliorative effect of *E. compressa* alcoholic and aqueous extracts in Ehrlich solid tumor induced mice. This goal was achieved through estimation of the biochemical parameters; aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, creatinine, and total antioxidant capacity (TAC) in mice serum. Evaluation of flavonoids and phenols was conducted in both extracts of *E. compressa*. In addition, histopathological examination was performed on tumor tissue, liver, kidney, and spleen of treated mice.

MATERIALS AND METHODS

1. Samples collection

Samples of seaweeds were collected from the substratum of the rock along the Mediterranean coast, Port Said, Egypt from March to June (2023), and then identified as *E. compressa* by professor Fekry Ashour Mourad (researcher at National institute of Oceanography and fisheries, Suez, Egypt). Collected algal samples were washed with seawater to remove sand particles. To avoid dryness, samples were transported immediately to the laboratory in plastic bags filled with seawater. Later, specimens were rinsed with tap water followed by distilled water to remove stuck substances and salts, then they were dried in an oven at 60°C **(Pradhan *et al*., 2021)**. After drying, they were cut into small pieces using a mortar and pestle, and finally ground into powder by an electric mixer.

2. Preparation of crude extract

2.1. Ethanolic extract

The powdered algae (500 g) were mixed with 95% ethanol and water (1:10) for 3 days with shaking, then filtered using four layers of gauze and subsequently re-filtered three times. After maceration and filtration, the filtrate was dried with a rotary

evaporator to yield a viscous crude ethanolic extract. Finally, the extracts were weighed and stored at -20°C until utilized **(Aziz & Noor, 2010)**.

2.2. Aqueous extract

According to the traditional method, dried algae (500g) were extracted using distilled water with some modifications. Powdered algae were filtered through four layers of gauze, followed by triple filtration. The extract was freeze-dried to obtain the crude form. The crude extract was maintained at -20ºC in sterilized bottles for further experimental use **(Ayache *et al*., 2020)**.

3. Determination of total flavonoids and phenols

3.1. Estimation of total phenolic content (TPC)

Gallic acid stock solution of 2mg/ ml was dissolved in methanol, then serial dilutions were prepared to obtain concentrations from 25 to 1000µg/ ml. Samples were prepared at a concentrations of 10mg/ ml in 95% ethanol and in distilled water. Measuring of total phenolic content is carried out by using the Folin–Ciocalteu method. Briefly, the procedure consisted of mixing 10µL of sample/standard with 100µL of Folin-Ciocalteu reagent (diluted 1: 10) in a 96-well microplate. Then, 80µL of 1M Na_2CO_3 was added and the mixture was incubated at room temperature (25°C) in the dark for 20 minutes. Absorbance was measured at 630nm using a microplate reader (FluoStar Omega, BMG Labtech, Germany) **(Albini *et al*., 2010)**.

3.2. Estimation of total flavonoid content (TFC)

Stock solution of Rutin at µg/mL in methanol was dissolved, and then serial dilutions were prepared to obtain the desired concentrations (from 15.62 to 1000µg/ ml). The total flavonoid content was determined using the aluminum chloride colorimetric method as described by **Herald *et al*. (2012)** with minor modifications to be carried out in microplates. Briefly, 15µL of sample/standard was placed in a 96-well microplate. Then, 175µL of methanol was added followed by 30µL of 1.25 % $AlCl_3$. Finally, 30µL of 0.125 $MC_2H_3NaO_2$ was added and incubated for 5 minutes. Absorbance was measured at 420nm and was recorded by using a microplate reader (FluoStar Omega, BMG Labtech, Germany).

4. Animals and experimental design

Seventy male albino mice, each weighing approximately 20–25 grams were used in the current study. The mice were housed under standard laboratory conditions for acclimatization prior to the experimental procedures in the animal house of Zoology Department, Faculty of Science, Port Said University. Mouse bearing Ehrlich Ascites Carcinoma (EAC) were purchased from National Cancer Institute, Cairo University, Giza, Egypt. 0.2ml of ascitic fluid was collected from the mouse peritoneal cavity and was diluted with saline. After 2 weeks, about 2×10^6 of EAC viable cells were injected intramuscularly into the left thigh of lower limb of each mouse. Solid tumor was developed within 6 days after inoculation, and all treatments were administered once every other day for 14 days. Mice were divided into seven groups (10 per each group) as

follow: Group I (negative control group): mice received 0.2ml of saline solution intraperitoneally (IP). The other sixty mice were injected with EAC cells until the tumor volume reached about 200mm^3 **(Lee *et al*., 2014, 2017)**; they were randomly divided into six groups. Group II EST- positive control group (untreated): mice were implanted with solid tumor and received IP 0.2ml 0.9% NaCl saline solution. Group III: EST-bearing mice were injected IP with 2mg/ kg of cisplatin **(Sedlar *et al*., 2012)**. Group IV (LD-Eth): mice were injected IP with a low dose of *E. compressa* ethanolic extract (100mg/ kg). Group V (HD-Eth): mice were injected IP with a high dose of *E. compressa* ethanolic extract (200 mg/kg). Group VI (LD-Aqu): mice were injected IP with a low dose of *E. compressa* aqueous extract (100mg/ kg). Group VII (HD-Aqu): mice were injected IP with a high dose of *E. compressa* aqueous extract (200mg/ kg) **(Abou-Elella & Ahmed, 2015)**.

5. Hematological assay

Blood samples were collected in ethylene diamine tetra acetic acid (EDTA) tubes from all mice groups for the determination of hemoglobin concentration (HB), red blood cells count (RBCs), white blood cells count (WBCs), hematocrit (PCV), mean corpuscular h**e**moglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), red cells distribution width (RDW), monocytes, lymphocytes, neutrophils, eosinophils and platelets. These parameters were assessed using Sysmex XN-550 automated hematology analyzer (Sysmex, Kobe, Japan).

6. Measurement of biochemical parameters

For biochemical analysis, blood samples were collected from mice of all experimental groups in plain tubes at the end of the experiment. Blood samples were centrifuged at 4000 rpm for 5min. After centrifugation, sera were separated to investigate the activities of AST, ALT, creatinine, and urea concentrations. These parameters were measured by a readymade kit produced by Clinichem Ltd (Budapest, Budafoki) using a spectrophotometer SCILOGEX (SCI-UV1000), based upon the manufacturer's guidelines.

7. Assessment of serum total antioxidant capacity (TAC)

TAC was measured in serum by ELISA method by a kit produced by Sunlong Biotech Co., LTD, China, using ELISA Reader (ELISA Reader: Hyperion 4 Plus MicroReader), according to manufacturer's procedures.

8. Histopathological examination

At the end of the experiment, mice were sacrificed and abdominally dissected. Consequently, tumor tissue, liver, kidney, and spleen were rapidly removed. Then, they were washed with saline solution (0.9% NaCl) to eliminate any residual blood that could disrupt the fixation process. Afterward, samples were fixed in 10% formalin for 24 hours to ensure adequate fixation. The step of dehydration and clearing of samples was routinely processed. Later, tissue samples were then embedded in paraffin wax, and sections with 5-micron thickness were cut with a microtome and mounted on glass slides.

These sections were then deparaffinized in xylene (two changes, 5 minutes each), rehydrated through a series of graded alcohols, and stained with hematoxylin and eosin (H&E) stain. The stained sections were then examined under a light microscope (ZEISS Primo Star) and photographed **(Elkotby *et al*., 2017)**. Samples of tumor tissue were examined to evaluate the levels of necrosis and inflammatory cell infiltration using a scoring method adapted from the Chevallier system which grades pathological response ranging from 1 (complete response) to 4 (minimal or no response) **(Chevallier *et al*., 1993)**. According to the degree of renal tubular damage, pathological changes in kidney were assessed and scored from 0 to +4 as follow: 0= absent , +1 = less than 25% of tubular damage, + 2 = 25%-50 % tubules damage, +3 = more than 50% of tubules showed evidence of damage, +4 = complete atrophy of the renal tubules **(Cao *et al*., 2000)**. Glomerular changes in the kidney were assessed according to the glomerular scoring system described by **Tervaert *et al*. (2010)**.

9. Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS 22.0) software. The values were exposed as mean values ± SEM and data were analyzed using one-way ANOVA, followed by Tukey's test. Statistical significance was assessed at $P< 0.05$.

10. Ethical approval

All animal experimental procedures were approved by the Research Ethics Committee of the Faculty of Science, Port Said University (Research code: ERN: PSU. Sci.116).

RESULTS

1. Determination of total flavonoids and phenols content

The total flavonoid and phenolic contents were evaluated and expressed as mg rutin equivalent (RE) and mg gallic acid equivalent (GAE) per gram of extract, respectively. Data revealed that the aqueous extract contained 10.551 ± 0.448 µg GA E/mg of total phenols and 7.899 ± 0.423 µg R E/mg of flavonoids, which were higher than those of the ethanolic extract (7.913 ± 0.336 µg GA E/mg and 5.924 ± 0.317 µg R E/mg, respectively) (Fig. 1).

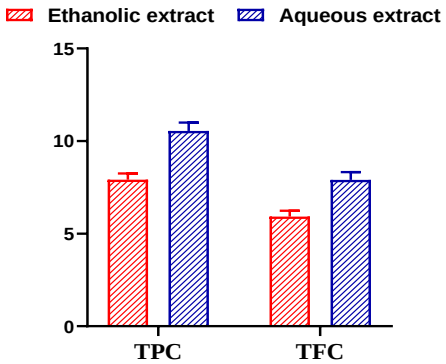

Fig. 1. Total phenolics (TPC) and total flavonoids (TFC) in ethanolic and aqueous extracts of *E. compressa*

2. Effect of *E. compressa* extracts on blood parameters of EST-bearing mice

2.1. Influence of E. compressa extracts on erythrocytic parameters

All EST-bearing mice groups treated with *E. compressa* extracts showed a significant decrease in erythrocytes count compared with EST-control group ($P< 0.05$). On the other hand, RBCs count was significantly increased in EST-control group in comparison with all treated groups and normal group as well ($P< 0.05$). A significant decrease in hemoglobin content in comparison with all treated groups and normal group was observed. Furthermore, PCV was significantly decreased in all treated group compared with an EST-control group ($P< 0.05$). Besides, a significant decrease in PCV was observed in all treatment groups compared with the normal group ($P<0.05$). However, non-significant differences were reported in the MCV, MCH, MCHC, and RDW values between all treated groups and the negative control group ($P> 0.05$) (Fig. 2A, B) and (Table 1).

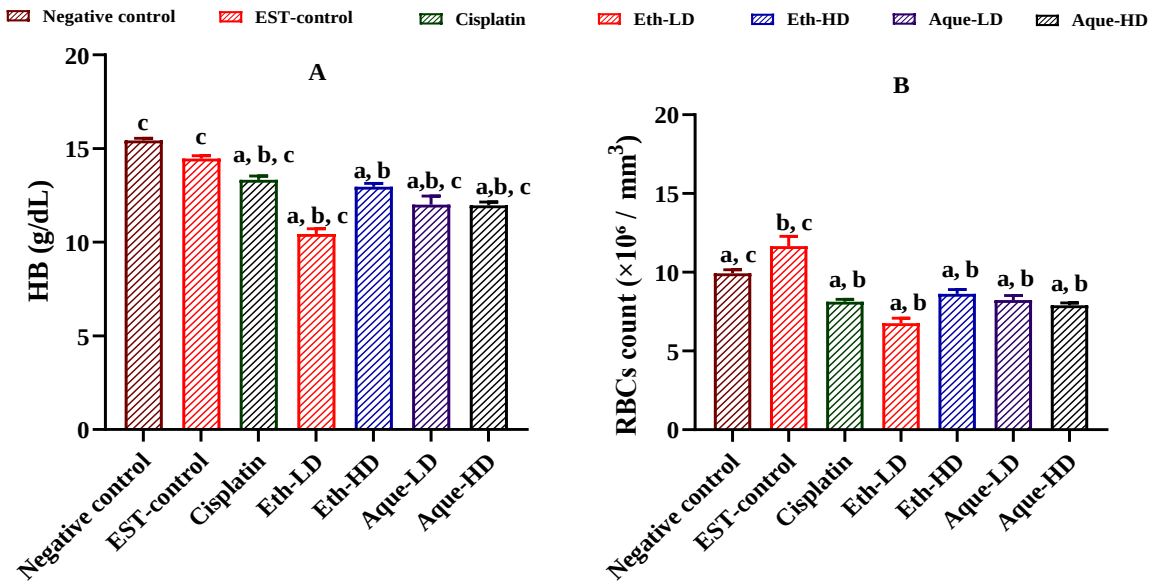

Fig. 2. Alterations in hemoglobin levels (A) and red blood cell count (B) in the blood of EST-bearing mice after 14 days of treatment with *E. compressa* extracts and cisplatin. Data are presented as mean ± SEM. Letters (a, b, c) indicate statistically significant differences ($P<0.05$) where [a] compared with positive control, [b] compared with negative control, and [c] compared with cisplatin treated groups using one-way ANOVA followed by Tukey's test).

Table 1. Effect of *E. compressa* extracts treatment on erythrocytic hematological parameters of EST-bearing mice

Parameter	Negative control	EST-control	Cisplatin	Eth-LD	Eth-HD	Aque-LD	Aque-HD
PCV (%)	52± 0.3 [a, b]	54 ± 2.5	47 ± 0.4 [a, b]	34± 0.2 [a, b, c]	43± 0.4 [a, b]	42 ± 0.5 [a, b]	40± 0.6 [a, b]
MCV (fl)	53 ± 0.4	48 ± 3.3	54.8 ± 0.4	53 ± 0.8	53± 0.3	51± 0.4	51± 0.3
MCH (pg)	16 ± 0.19	15 ± 0.2	17 ± 0.03	15.7 ± 0.1	16± 0.1	15± 0.6	15 ± 0.2
MCHC (g/dl)	30 ± 0.3	28.8 ± 0.4	29.5 ± 0.2	30.3 ± 0.66	30± 0.5	29± 0.6 [c]	29± 0.4 [c]
RDW (%)	19 ± 0.3[c]	21 ± 0.3 [c]	17 ± 0.4 [a, b]	21± 0.6 [c, b]	18± 0.4[a]	20± 0.4 [c, b]	18± 0.3 [a]

All values are presented as mean ± SEM. Distinct letters (a, b, c) showed the significant differences at $P<0.05$, where ([a] versus positive control, [b] versus negative control and [c] versus cisplatin treated groups using one-way ANOVA followed by Tukey's test).

2.2. Influence of E. compressa extracts on total WBCs count

Total number of leukocytes in all treated groups and the EST-control group were significantly increased compared to the normal control group ($P<0.05$). The treatment with ethanolic and aqueous extracts of *E. compressa* extracts caused a significant reduction in the total WBCs count in all treated groups in comparison with the untreated EST-control group ($P< 0.05$) (Fig. 3A). Significant decreases in the counts of neutrophils and lymphocytes were observed in all treated groups compared with the untreated EST-control group (Fig. 3C, D).

2.3. Influence of E. compressa extracts on the total platelets count

Platelets count was significantly increased in the EST-control untreated group compared to the negative control group ($P< 0.05$). There were non-significant changes in platelet count in all treated groups and the normal group ($P> 0.05$). Meanwhile, platelet count revealed a significant decrease in all groups in comparison with the untreated EST-control group ($P< 0.05$) (Fig. 4).

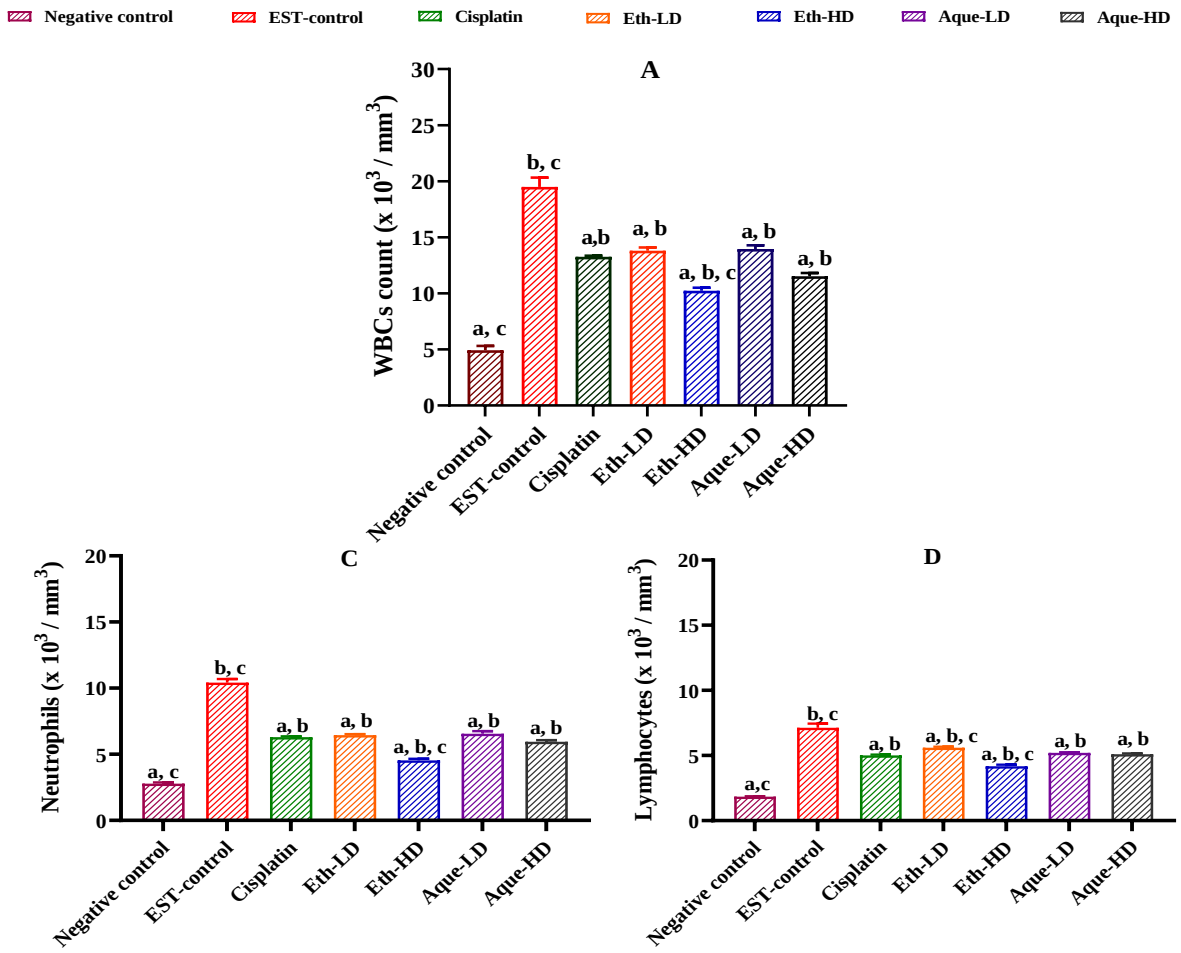

Fig. 3. Alternations in WBCs count (A), neutrophils count (C), and lymphocytes conut (D) in the blood of EST-bearing mice after 14 days of treatment with differennt doses of *E. compressa* extracts and cisplatin. Data are presented as mean ± SEM. Letters (a, b, c) indicate statistically significant differences (P<0.05) between groups where [a] compared with positive control, [b] versus negative control, and [c] versus cisplatin treated groups using one-way ANOVA followed by Tukey's test.

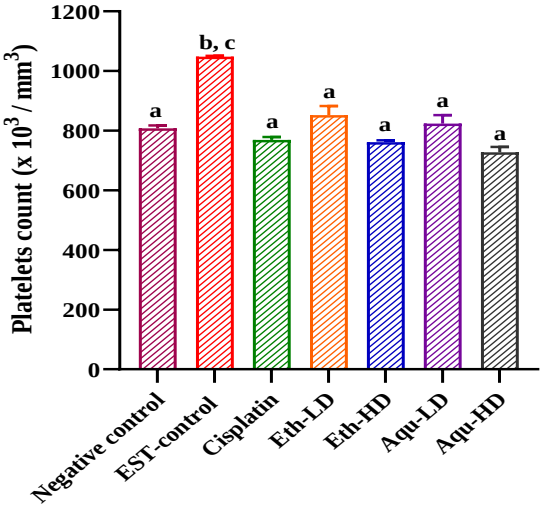

Fig. 4. Alternations in platelets count in the blood of EST-bearing mice after 14 days of treatment with differennt doses of *E. compressa* extracts and cisplatin. Data are presented as mean ± SEM. Letters (a, b, c) indicate statistically significant differences (P<0.05) where [a] compared with positive control group, [b] versus negative control group, and [c] versus cisplatin treated group using one-way ANOVA followed by Tukey's test.

3. Effect of *E. compressa* extracts on serum biochemical parameters

The liver enzymes ALT and AST in addition to the renal biomarkers urea and creatinine were measured in serum after 14 days of treatment. The levels of serum ALT, AST, urea and creatinine were significantly increased in untreated EST-control group in comparison with the negative control group ($P< 0.05$). On the other hand, these parameters were significantly decreased in all treated groups compared to the untreated EST-control group ($P<0.05$) (Fig. 5).

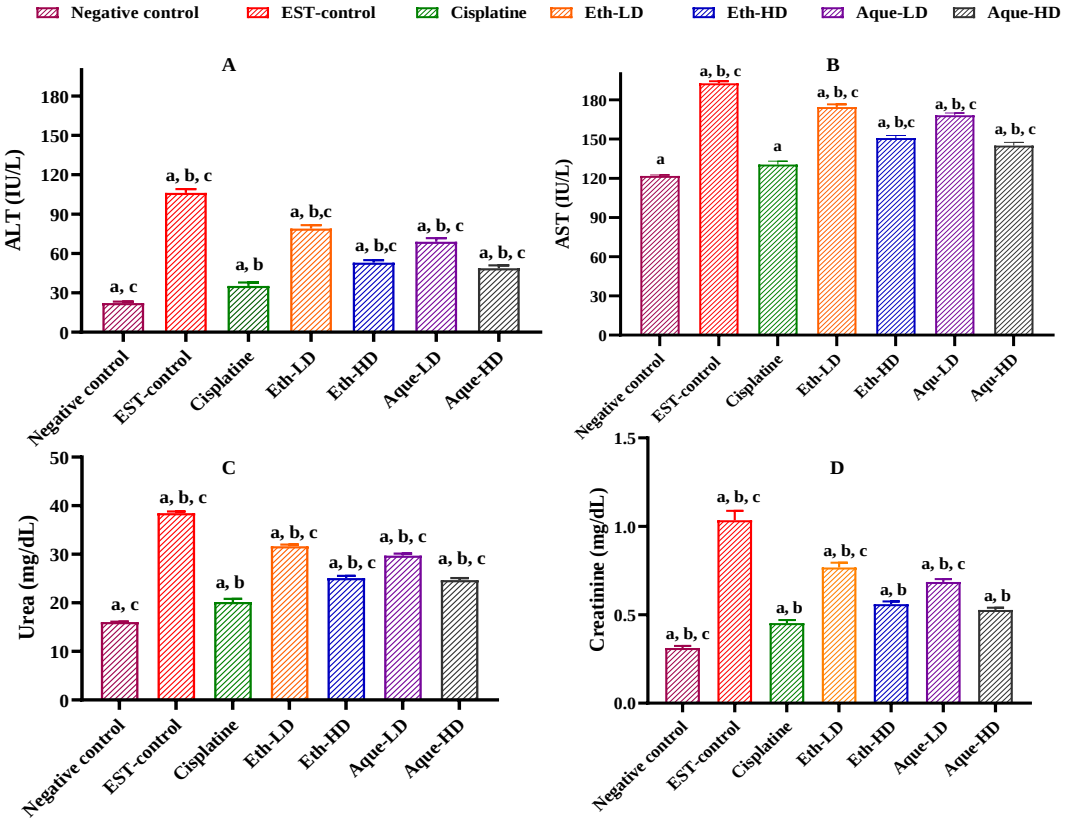

Fig. 5. Effect of *E. compressa* extracts and cisplatin on serum ALT, AST, urea, and creatinine of EST-bearing mice after 14 days of treatment (A, B, C, and D respectively). All values are presented as means ± SEM. Super scripted letters (a, b, c) refer to significant differences at $P<0.05$ where [a] versus positive control, [b] versus negative control and [c] versus cisplatin treated groups using one-way ANOVA followed by Tukey's test.

4. Determination of serum antioxidant capacity (TAC)

The levels of TAC were significantly decreased ($P< 0.05$) in untreated EST-control group (0.029 ± 0.0005 µmol/ml) compared to the negative control group (0.058 ± 0.0005 µmol/ml) ($P< 0.05$). In contrast, in Eth-LD, Eth-HD, Aqu-LD, Aqu-LD, and cisplatin treated groups, levels of TAC (0.052 ± 0.0008 µmol/ml, 0.035 ± 0.0004 µmol/ml, 0.043 ± 0.0004 µmol/ml, 0.038 ± 0.0006 µmol/ml, and 0.048 ± 0.0004 µmol/ml, respectively) were increased significantly ($P< 0.05$) compared with untreated EST-control (Figure 6).

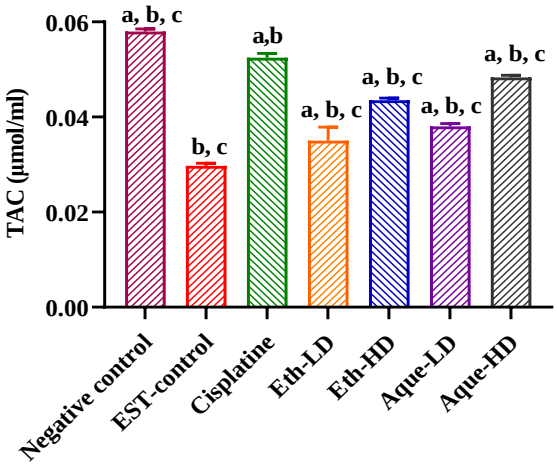

Fig. 6. Effect of *E. compressa* extracts and cisplatin on TAC levels of EST-bearing mice after 14 days of treatment. All values are presented as mean ± SEM. Super scripted letters a, b, and c are referring to significant differences between groups at $P<0.05$ where [a] versus positive control, [b] versus negative control, and [c] versus cisplatin treated groups using one-way ANOVA followed by Tukey's test.

5. Histopathological examination of the effect of *E. compressa* extracts on liver, kidney, spleen, and tumor tissue of treated mice

5.1. Histopathological examination of tumor tissues of thigh skeletal muscle

Thigh muscle sections examination of the normal mice group revealed a well-organized skeletal muscle bundles with typical muscle fiber morphology (Fig. 7A). Conversely, tumor tissue of the untreated EST mice showed an existence of markedly atypical cohesive epithelial cells with marked cellular, nuclear pleomorphism, hyperchromasia and increased nucleo-cytoplasmic ratio in solid groups and sheets with noticeable infiltrating of muscle bundles with tumor cells (score 3) (Fig. 7B). Whereas, cisplatin treated group showed better architecture and cytological features with areas of necrosis and chronic inflammatory cells infiltrate (score 1) (Fig. 7C). Furthermore, in EST-group treated with low dose of the ethanolic extract, tumor tissue showed poor architectural differentiation in tumor cells, and tumor cells infiltrated the skeletal muscle bundles; nonetheless, no necrotic areas could be observed (score 3) (Fig. 7D). On the contrary, better differentiation in the architecture features in the form of glandular-like structures, with areas of necrosis and infiltration of muscle bundles were noticed in the high dose ethanolic extract treated group (score 2) (Fig. 7E). A better cytological differentiation, a decrease in cytological atypia, and muscle bundles infiltration were observed in the both doses of aqueous extract treated groups (Fig. 7F, G). Amazingly, more than 90 % of tumor cells were necrotic in the high dose aqueous extract treated group (score 1). In addition, the low dose of aqueous extract treated group caused tumor cell necrosis in a percentage of 50-90% (score 2).

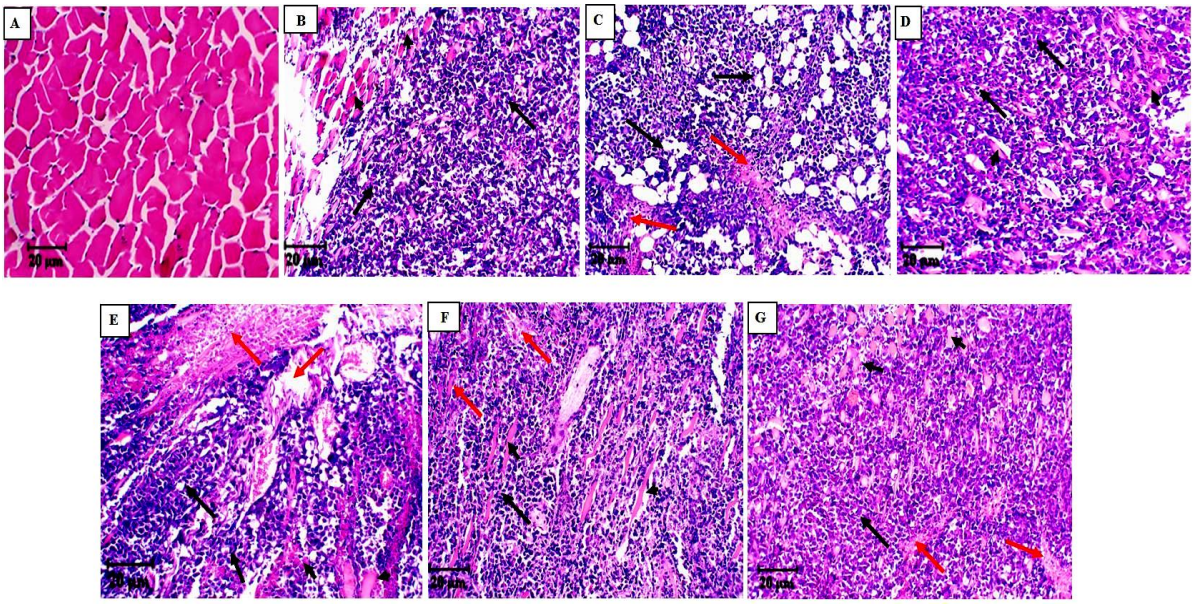

Fig. 7. Photomicrographs of thigh skeletal muscle sections stained by hematoxylin and eosin (20x). (A) Normal control group. (B) Untreated EST-control group. (C) EST group treated with cisplatin (D) Low dose ethanolic extract treated group. (E) High dose ethanolic extract treated group. (F) Low dose aqueous extract treated group. (G) High dose aqueous extract treated group. The black arrows indicate tumor tissue cells, areas of necrosis are indicated by the red arrows, and infiltration of muscle bundles is indicated by the black arrowheads.

5.2. Effect of E. compressa extracts treatment on the liver of EST-bearing mice

Histopathological examination of the negative control group showed preserved hepatic normal architecture. The liver parenchyma is consisted of well-organized lobules with a central vein and a uniform portal tract. The identical hepatocytes are polygonal in shape with eosinophilic cytoplasm and a large spherical nucleus (Fig. 8A). In the positive control group, an evidence of liver injury was distinguished accompanied with lymphocytic infiltrate within the sinusoid and areas of lytic necrosis, which are replaced with inflammatory cells. Scattered, injured, swollen hepatocytes were also observed (Fig. 8B). Moreover, centri-lobular inflammation with an area of lytic necrosis, portal tract inflammation, and non-lymphocytic infiltration within sinusoids were observed in the cisplatin treated group (Fig. 8C). Ethanolic extract treated groups with different doses revealed lymphocytic infiltrate within sinusoid, and areas of lytic necrosis with inflammatory cells infiltration. In addition, no injured or swollen hepatocytes and foci of centri-lobular inflammation were observed in the low and high dose ethanolic extract treated groups (Fig. 8D, E). Wonderfully, a uniform liver tissue with no evidence of liver injury was noticed in the low and high doses aqueous extract treated group (Fig. 8F, G).

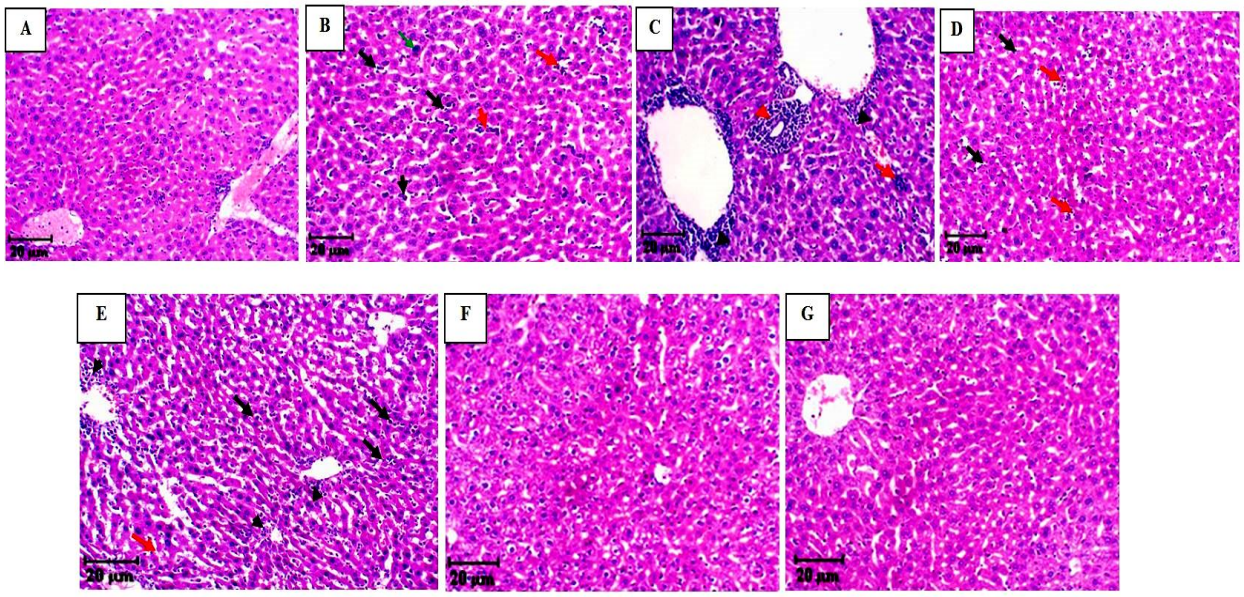

Fig. 8. Photomicrographs of liver sections stained by hematoxylin and eosin (20x). (A) Normal control group. (B) Untreated EST group. (C) Cisplatin treated group. (D) Low dose ethanolic extract treated group. (E) High dose ethanolic extract treated group. (F) Low dose aqueous extract treated group. (G) High dose aqueous extract treated group. The black arrows are referring to lymphocytic infiltrate. The red arrows are referring to areas of lytic necrosis replaced with inflammatory cells. The green arrows are referring to scattered, injured, and swollen hepatocytes. The black arrowheads are referring to foci of centri-lobular inflammation. The red arrowheads are referring to portal tract inflammation.

5.3. Effect of E. compressa extracts on the kidney of EST-bearing mice

Examination of the healthy group kidneys showed normal renal tissue architecture, glomeruli and tubules. Proximal convoluted tubules (PCT) are lined with cuboidal epithelial cells and a well-preserved brush border. Distal convoluted tubules with low cuboidal to flattened epithelial cells and distinct uniform lumens (Fig. 9A). In the untreated control group, an acute tubular injury induced a thickness of epithelial cells and its basement membrane. Additionally, necrotic cells with cytoplasmic vacuolization and blebbing in more than 50% of renal tubules (grade +3) were observed. Moreover, mild mesangial expansion in < 25% of the observed scattered glomeruli was remarked (Fig. 9B). In cisplatin treated group, a uniform renal tissue, glomeruli and tubules were noticed (Fig. 9C). In ethanolic extract treated groups, few tubules showed an evidence of acute tubular injury (grade +1) in which glomeruli were diffused and enlarged with mesangial cells proliferation and mild mesangium expansion (> 25%). The tubular injury was attended with congestion in blood vessels within interstetium has been observed in low dose ethanolic extract treated group (Fig. 9D, E). Treatment with the low and high doses of aqueous extract showed no evidence of acute tubular injury, but few glomeruli showed mild mesangium expansion in less than 25% of tubules (Fig. 9F, G).

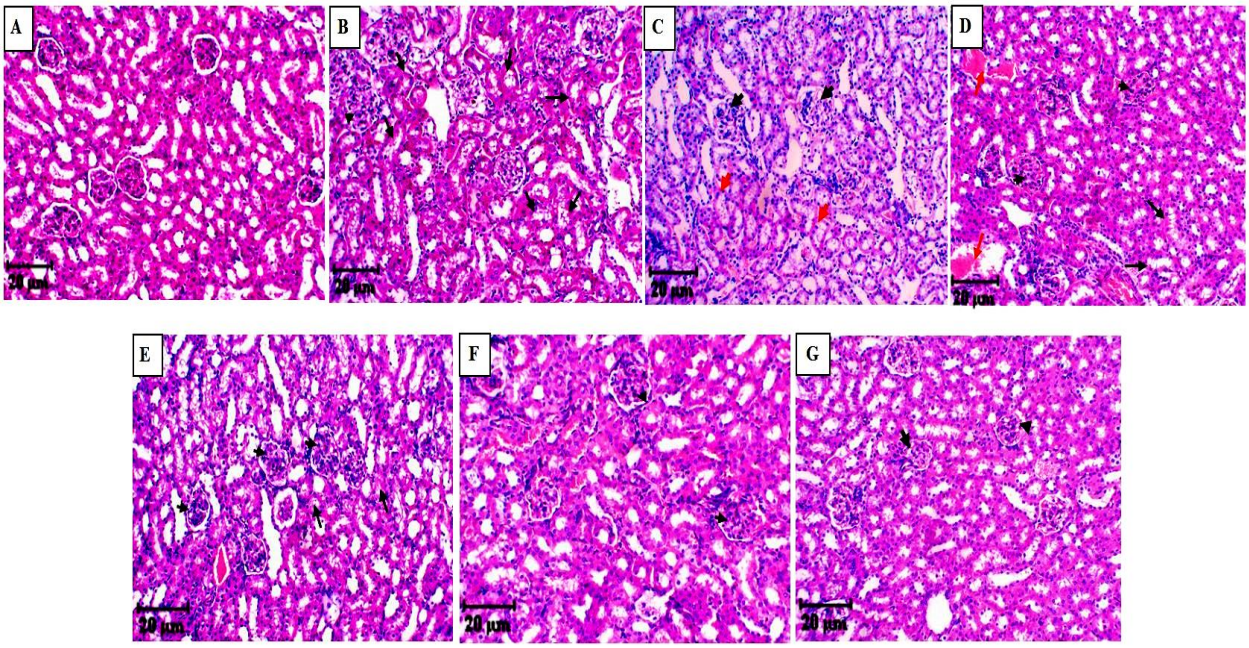

Fig. 9. Photomicrographs of kidney sections stained by hematoxylin and eosin (20x). (A) Normal control group. (B) Untreated EST-control group. (C) Cisplatin treated group. (D) Low dose ethanolic extract treated group (E) High dose ethanolic extract treated group. (F) Low dose aqueous extract treated group. (G) High dose aqueous extract treated group. Acute tubular injury (Black arrows). Mesangial expansion of glomeruli (Black arrowheads). Congested blood vessels (Red arrowheads).

5.4. Effect of E. compressa extracts on the spleen of EST-bearing mice

Spleen sections of the normal control group showed a uniform splenic tissue with clearly defined white and red pulp (Fig. 10A). The untreated EST-control group displayed compressed white pulp with an expansion and congestion of red pulp (Fig. 10B). The normal architecture of the white pulp, and the red pulp was restored in all treated groups (Fig. 10C, E, F and G), except in the ethanolic extract low dose treated group, which exposed a slight disturbance in the splenic architecture with an expansion and slight congestion of the white and red pulps (Fig. 10D).

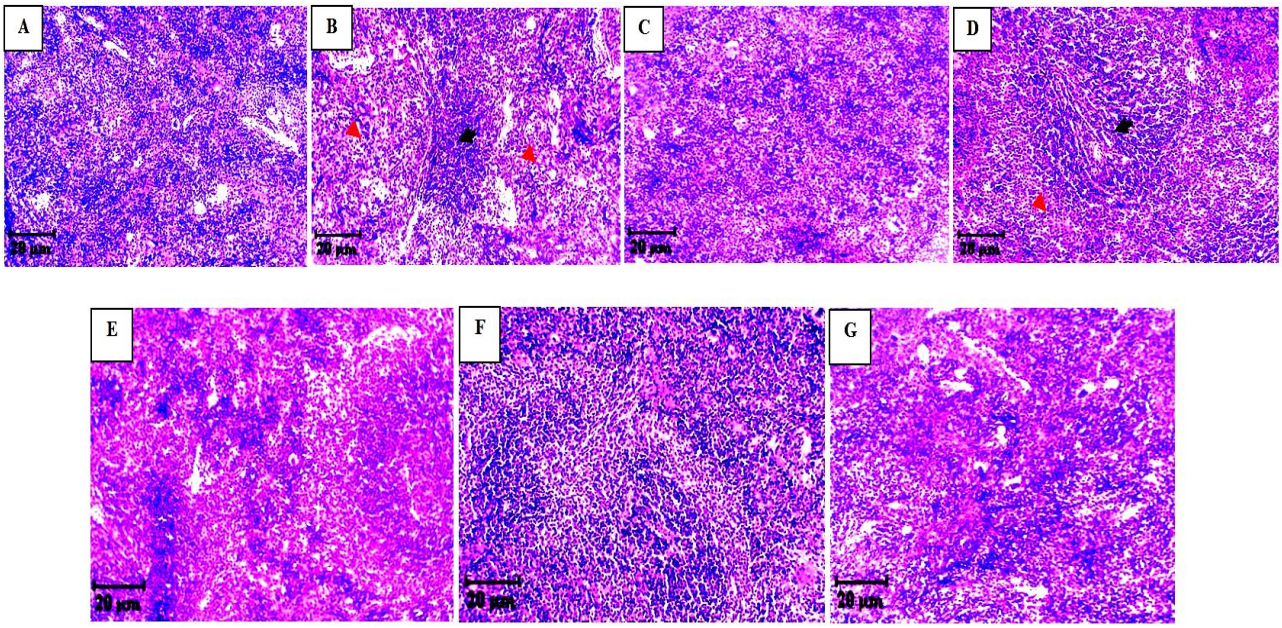

Fig. 10. Photomicrographs of spleen sections stained by hematoxylin and eosin (20x). (A) normal control group. (B) Untreated EST-control group. (C) Cisplatin treated group. (D) Low dose ethanolic extract treated group. (E) High dose ethanolic extract treated group. (F) Low dose aqueous extract treated group. (G) High dose aqueous extract treated group. Congestion of the red pulb (Red arrowheads). Compressed white pulp (Black arrowheads).

DISCUSSION

For thousands of years ago, naturally derived constituents have been recognized as the main sources of numerous developed drugs and therapeutic agents. These products were derived from fungi, algae, plants, and animal-derived extracts whether in the form of crude extracts or traditional preparations. Furthermore, they have a well-established key role in the management of various human diseases as cancer and many infectious diseases. Moreover, the majority of FDA-approved drugs are either directly or indirectly originated from natural sources **(Patridge *et al*., 2016)**. Despite the increasing prevalence of synthetic drugs owing to their noticeable therapeutic outcomes, time performance, and regarding their safety, this raised concerns, leading to increased reliance on natural products.

Algae, particularly marine macroalgae (seaweeds), are a group with wide biological variations. Marine macroalgae produce a wide array of primary and secondary metabolites as phenolic compounds, flavonoids, peptides, fatty acids, vitamins, minerals, polysaccharides, and pigments. The therapeutic potential of algae has garnered significant interest from researchers due to their antioxidant, anti-inflammatory, anticancer, antidiabetic, and antiviral activities **(Abo-Shady *et al*., 2023)**. Various studies have highlighted that polysaccharides extracted from seaweeds such as carrageenans, galactan, and fucoidan possess strong anticancer, antioxidant, and anti-inflammatory properties as well **(Carrasqueira *et al*., 2025)**. Fucoidan could inhibits tumor growth by inducing cell

cycle arrest and apoptosis, preventing metastasis, and regulating physiological signaling pathways **(Duan *et al*., 2020)**. Additionally, polysaccharides extracted from the green alga *Ulva conglobate,* a member of the same family of *E. compressa*, possessed antioxidant properties **(Yang *et al*., 2021)**.

The health-promoting effects of algae are not limited to polysaccharides lone, the presence of fatty acids, phenolic compounds, and flavonoids participate in their antioxidant, anti-inflammatory, and anticancer activities **(Goutzourelas *et al*., 2023)**. Furthermore, seaweeds contain fatty acids as polyunsaturated fatty acids (PUFAs) and saturated fatty acids (SFAs). Several studies have reported that PUFAs from *Ulva* sp. exhibit anticancer activity, in addition to their anti-inflammatory activity **(Khalil Mohamed *et al*., 2023)**. Likewise, according to **Korzeniowska *et al*. (2020)**, phenolic compounds that were identified in macroalgae as p-coumaric, gallic, and chlorogenic acids were also found in the green alga *Cladophora glomerata*, which contribute to its antioxidant activity. In addition, flavonoids as quercetin, rutin, and kaempferol were detected in some algal species, and showed anticancer and antioxidant properties **(Korzeniowska *et al*., 2020; Mahendran *et al*., 2024)**.

E. compressa is a green alga that belongs to Ulvaceae family and is broadly distributed along Mediterranean Sea. It has recognized by its biological activities as anticancer, antidiabetic, anti-inflammatory and antimicrobial agents **(Pradhan *et al*., 2022)**. Considering the well-documented bioactive properties of flavonoid and phenolic compounds, the present study revealed that aqueous and ethanolic extracts of *E. compressa* exhibited detectable amounts of flavonoids and phenols. This finding is in agreement with previously published studies who confirmed that different extracts of *E. compressa* demonstrated the presence of flavonoids and phenolic constituents **(Abou Gabal *et al*., 2021; Jothi & Jayaprakash, 2022)**.

Antioxidants derived from marine organisms as algae, have drawn significant attention in scientific research due to their capacity to neutralize reactive oxygen species (ROS) by serving as electron donors or acceptors. By attenuating oxidative stress, these metabolites may mitigate ROS-mediated cellular injury, which is a critical factor in the pathogenesis of inflammatory diseases, cancer, and diabetes. The intrinsic mitochondrial apoptotic pathway is controlled by the Bcl-2 family, in which Bcl-2 serves as an anti-apoptotic protein, while Bax is a pro-apoptotic mediator. Some marine-derived substances trigger apoptosis by up-regulating Bax expression which increases the permeability of the mitochondrial membrane and leads to leakage of cytochrome c, and ultimately activating caspase-dependent cell death. Conversely, other marine metabolites can induce apoptosis by down-regulation of Bcl-2 protein **(Abuzahrah *et al*., 2025)**. Additionally, BH3-only proteins influence this process by activating Bax or inhibiting Bcl-2, thereby shifting the cellular balance toward apoptosis. In the inflammation process, antioxidants lower oxidative stress, which is a key factor in the activation of the nuclear factor (NF-kB) and mitogen-activated protein kinases (MAPKs), which promote the production of pro-

inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) **(Chaudhary *et al*., 2023)**.

Reliable laboratory tests for liver functions such as ALT and AST are essential biomarkers for the early diagnosis and monitoring of liver injury and diseases. Metabolism in normal liver may be affected by induced Ehrlich solid tumor, which may cause hepatocellular damage and alternations in hepatocytes permeability resulted in elevated levels of serum ALT and AST **(Elkholy *et al*., 2022)**. This may elucidate the reason for the significant increase in these biochemical parameters in untreated EST-control group compared with negative control group in the current study. Creatinine and urea are considered common laboratory tests for detecting renal function deficiency. In the present study, serum urea and creatinine levels were significantly increased in the untreated EST-control group compared to the negative control group. Previous study has reported that Ehrlich tumors may induce adverse abnormal effects in the kidney function causing increased concentrations of serum creatinine and urea **(Abd Eldaim *et al*., 2019)**. Similarly**,** in the current work, serum creatinine and urea concentrations of the untreated EST-control group were increased. A previous study has reported that treatment with different extracts of Ulvaceae family exhibited a decline in these biochemical parameters **(Abdelaziz *et al*., 2023)**. These findings indicate that the algal extracts may possess renal and hepato-protective properties which could be attributed to their active antioxidant constituents **(El Gamal, 2010)**. The presence of flavonoids and phenolic compounds in both extracts supports the observed enhancement in TAC, indicating that these bioactive compounds contribute to the antioxidant activity, thereby clarifying the significant decrease in the liver enzymes in all treated groups with *E. compressa* extracts compared with the untreated EST-control group. Beside phenolic and flavonoid, other bioactive molecules as fatty acids, terpenoids, and carotenoids which are found in *E. compressa* extracts and may contribute to the observed bioactivities **(Sona, 2023)**. These bioactive compounds may play a vital role in antioxidant activity and also exhibit anticancer potential through increasing expression of Bax gene **(Abou-Elella & Ahmed, 2015)**. Moreover, several studies have revealed that *E. compressa* extracts exhibited antioxidant activity in tumor-bearing mice by modulating of ROS resulted from several types of cancer **(Abd-Ellatef *et al*., 2017)**.

Furthermore, these biochemical data is in align with the histopathological examination hence adverse abnormal effects were observed in the liver sections of untreated EST-control group with marked evidences of hepatic injury; accordingly, liver enzymes have been increased.

Histopathological finding in the ethanolic extract treated group revealed an infiltration with lymphocytes into hepatic sinusoids and lytic necrotic areas with inflammatory cells. Furthermore, kidney histological examination showed an evidence of tubular injury and glomerular mesangial expansion in untreated EST-control group. These pathological alternations were ameliorated after treatment with *E. compressa* extracts. Similarly, this

finding is matching with biochemical results of creatinine and urea concentrations which have been increased in untreated EST group and significantly declined after treatment by different extracts of *E. compressa*. Wonderfully, high and low doses of aqueous extract treated groups showed the finest improvement in kidney and liver tissues; hence, neither liver nor renal tissues were invaded with metastatic atypical tumor cells. These results are in consistent with the mentioned elevated biochemical values in the untreated EST-control group and their improvement after treatment. Similar improvement had been revealed in tumor tissue in all treated groups relative to malignant epithelial cells with infiltrating of muscle bundles which were shown in EST-control group. Moreover, spleen histological examination showed recovery of normal white and red splenic pulp in all treated groups with no marked effect in low dose ethanolic treated group referred to atrophy of white pulp, vascular dilation of red pulp compared with EST-control group. This improvement could be attributed to the protective antioxidant properties of *E. compressa* **(Pradhan *et al*., 2020)**.

The complete blood picture (CBC) is a common and simple lab test that offers comprehensive insight about an individual's health. Efficient analysis of this test is a valid and pivotal tool for early diagnosis of various health disorders as cancer and immunologic disorders, which are necessary for further validation through detailed laboratory and assessment. Cancer pathogenesis has adverse effects on haematological parameters **(Berta *et al*., 2024)**. These abnormalities in CBC are correlated with malignant cell infiltration in different organs **(Wassie *et al*., 2021)**. In the present study, a significant increase in RBCs count in the EST-control group compared with all treated groups as well as normal control group was reported. After treatment with the different extracts, compared with untreated EST-control group, a significant decrease was observed in RBCs count in all treated groups. These results could be initiated by abnormal immune responses or the ectopic secretion of biologically active substances, including hormones, cytokines, and peptides in some cancer types like in renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC**)** which is known as paraneoplastic syndrome **(Pare & Tamilia, 2021)**. Hence, Ehrlich ascites carcinoma cells may be infiltrated into distant tissues. These may be clarified by the histological examination of kidney and liver and elevated levels in biochemical parameters in the untreated EST-control group. Due to paraneoplastic, polycythemia, HB content, PCV were significantly increased in untreated EST-control group in comparison with all treated group.

Diagnosis of a wide range of cancer types and tumor growth is commonly associated with spontaneous leukocytosis and thrombocytosis **(Kohutek *et al*., 2018)**. In the present study, total WBCs and platelets count was elevated in the untreated EST-control group. Upon treatment with different doses of *E. compressa* extracts, a prominent recovery of the total WBCs count was almost nearby the limits of normal ranges. In addition, a decreasing in platelets count was reported in comparison with the positive control group. Reduction of total blood WBCs count and circulating platelet count is a hallmark

manifestation of oncologic therapeutics, which suppresses the tumorigenesis in tumor-bearing animals **(Buergy *et al.*, 2012)**. This hematological finding and ameliorative effects in the biochemical and histopathological alterations following the treatment with different doses of *E. compressa* extracts could be evidences for the protective and anticancer activity of them.

CONCLUSION

The present study revealed the effect of *E. compressa* ethanolic and aqueous extracts in Ehrlich solid tumor-bearing mice treatment regarding tissues examination, biochemical and hematological parameters. Treatment with all extracts at different doses possessed improving effects based on the action of bioactive phenols and flavonoids contents of the extracts which improve the total antioxidant capacity in treated mice. Biochemical findings and histopathological examination of tumor tissues have confirmed the ameliorative effects on the treated mice compared with untreated EST-bearing mice.

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