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The Antioxidant, Anti-inflammatory and Hepatoprotective Effects of the Sea Anemone Extract Against Induced Hepatotoxicity

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ABSTRACT

5 Fluorouracil® (5-FU) is a commonly used anticancer medication that works by preventing the replication of the DNA. While 5-FU's adverse effects are extensively reported, the mechanism underlying 5-FU's hepatotoxic effects remains unclear. The aim of this investigation was to assess the potential antioxidant; anti-inflammatory and hepatoprotective mechanism of sea anemone extract (SE) induced hepatotoxicity. Four groups of animals were randomly assigned as follows: 1) Healthy reference group; 2) Oral administration of SE (50mg/ kg/ day) to healthy rats; 3) Hepatotoxicity model animals, and 4) hepatotoxicity model animals receiving SE. Results showed that SE was able to reduce hepatotoxicity after six weeks of therapy; this was demonstrated by a marked increase in albumin and total protein as well as hepatic GSH, SOD, and CAT values, along with a significant decrease in serum ALAT, ASAT, GGT, ALP, bilirubin, TNF-α, IL-1β, IL-4, IL-6, IL-10, and AFP values. These effects significantly reduced hepatic MDA, NO, and DNA fragmentation. It can be concluded that SE was highly successful in mitigating the oxidative stress caused by hepatotoxicity and shielding the liver from its harmful effects. As such, SE is a promising supplement candidate for shielding the liver from the negative effects of chemotherapy medications.

INTRODUCTION

These days, cancer is a major global public health concern **(Siegel *et al*., 2019)**. There are several approaches used in the treatment of cancer, including surgery, radiation, and chemotherapy. One effective treatment for cancer and anti-tumor medicines is chemotherapy. For this reason, 5-Fluorouracil® (5-FU) is a frequently used medication in the treatment of a number of cancers, including head and neck, colon, and breast cancer **(Akindele *et al*., 2018)**. 5-FU has several benefits, but its use has been severely restricted because of organ toxicity, thymine synthesis suppression, and DNA damage **(Akindele *et al*., 2018)**. When considering the mechanism of action of 5-FU, it is known to impact the

S phase of the cell cycle, activate thymidine phosphorylase, and block fluorodeoxyuridine by thymidylate synthase. As a result, it stops DNA synthesis which kills cells **(Gelen *et al*., 2017)**. Only a small amount of 5-FU is eliminated by the kidney; the liver eliminates the majority of it **(Longley *et al*., 2003)**. The frequency of drug-induced hepatotoxicity and nephrotoxicity is rising, and among these medications are anticancer agents **(Abdel-Daim *et al*., 2019; Sengul *et al*., 2021)** . Similar to other anticancer drugs, 5-FU induces oxidative stress, inflammation, and apoptosis in the liver and kidneys, as well as toxicity and dysfunction in these tissues **(Gelen *et al*., 2018)**.

Extreme circumstances, such as ultraviolet (UV) light and variable temperature, salinity, and dissolved oxygen, are characteristics of animals that live in highly dynamic habitats, such as shallow estuary environments and tropical and subtropical coastal intertidal environments **(Dyshlovoy & Honecker, 2019)**. Marine invertebrates, like sponges and cnidarians, are thought to be a promising source of special bioactive compounds because of these harsh conditions. These compounds could be used in biotechnology for a variety of purposes, including nutritional supplements, pharmaceutical drugs, cosmetics, and even the prevention and treatment of human diseases **(Mayer *et al*., 2017; Brunt & Burgess, 2018)**. Thus, sixteen medications that were developed from naturally occurring marine-derived compounds are currently authorized for use in patients. Eleven out of sixteen of these medications are used to treat various forms of cancer in humans **(Mayer *et al*., 2021)**. Additionally, an astounding range of dietary supplements made from the extracts and semi-purified fraction of consumable marine species have been shown to have positive effects on human health **(Suleria *et al*., 2015)**. Numerous of them were thought to possess immunostimulatory, antioxidant, and cancer-preventive qualities **(Petri *et al*., 2020)**. An important source of a complex mixture of bioactive components, such as amino acids, polypeptides, and other chemicals that are employed as antibiotic, anticancer, and anti-inflammatory drugs, has been reported to be anthozoans such as sea anemones **(Rocha *et al*., 2011)**.

Moreover, an astounding range of dietary supplements made from the semi-purified fraction and extracts of edible marine species have been created, and they have been shown to be helpful to human health **(Suleria *et al*., 2015)**. Numerous of them were thought to possess immunostimulatory, antioxidant, and cancer-preventive qualities **(Petri *et al*., 2020)**.

The species *Nematostella vectensis* (sea anemone), also known as the starlet sea anemone, is a member of the class *Anthozoa* and phylum *Cnidaria*; the group *Cnidaria*, which also comprises jellyfish, hydra, and corals. The starlet sea anemones are found throughout the North Atlantic coast of the United States and Canada, as well as the southeast coast of England. They usually live in the mud of estuary habitats, such as brackish water and salt marshes. The starlet sea anemone is typically exposed to extremely variable salinities (~ 2 to ~ 52 ‰) and temperatures (-1 to ~ 33ºC) in its natural habitat **(Kneib, 1988; Sheader *et al*., 1997)**. *Nematostella vectensis*, a lower

metazoan, has become a highly effective animal model system for numerous investigations on development, regeneration, and evolution within the last 20 years **(Stefanik *et al*., 2013)**.

The purpose of this study was to assess how well the sea anemone extract (SE) protects the liver from hepatotoxicity caused by 5-Fluorouracil® by acting as an antioxidant and anti-inflammatory.

MATERIALS AND METHODS

1. Chemicals

The United Company for Drugs, Assuit, Egypt, was the supplier of 5-fluorouracil®.

2. Specimen collection and extraction

Mikhail V. Matz (University of Texas at Austain, TX, USA) kindly gifted adult *Nematostella vectensis.* Three times a week, they were given freshly hatched *Artemia nauplii* and cultured in approximately one-third natural sea water. The sea anemones were starved for three days prior to the clumsy body removals. Following a dissection and small-piece cutting process, the entire animal was suspended in 2% acetic acid. The suspension underwent a 5-minute, 500g centrifugation at 4°C. Three times, the pellet was extracted again using 2% acetic acid. Before being used, the supernatant was lyophilized and kept at -80˚C.

3. HPLC analysis of phenolic constituents

An Agilent 1260 series was used for the HPLC analysis. Using a Kromasil C18 column (4.6mm x 250mm id, 5µm), the separation was performed. At a flow rate of one milliliter per minute, the mobile phase was composed of water (A) and 0.05% trifluoro-acetic acid in acetonitrile (B). The following was the sequential linear gradient programming for the mobile phase: 0 minutes (82% A), 0–5 minutes (80% A), 5-8 minutes (60% A), 8–12 minutes (60% A), 12–15 minutes (85% A), and 15–16 minutes (82% A). At 280nm, the multi-wavelength detector was observed. For every sample solution, there was one injection volume of ten microliters. The temperature of the column was kept constant at 35°C.

4. Animals and experimental design

A total of forty mature animals were acquired from the Animal Colony at the National Research Center in Egypt. The rats were housed in a temperature-controlled environment with a 12 hour light/dark cycle and free access to food and water for a week prior to the commencement of the experiment to allow for acclimatization. The Ethics Committee of the Science Faculty at Al-Azhar University in Assuit, Egypt, authorized the protocols used to provide the animals with human care in accordance with the institution's normal requirements. Following their acclimation to the circumstances of the experimental room, the animals were randomly assigned to four groups, each consisting of ten individuals: Group 1) healthy control rats were given 0.5 milliliters of water orally

every six weeks, Group 2): The sea anemone extract (50mg/ kg/ day) was given orally to healthy rats for a period of six weeks, Group 3): For six weeks, healthy rats were intraperitoneally given 125mg/ kg/ week of 5-Fluorouracil®, and group 4): Animal given the indicated dosages of 5-Fluorouracil® intoxication for six weeks together with SE intake.

5. Blood and tissue sampling

All animals were weighed at the conclusion of the treatment period, fasted for the entire night, and then blood was extracted from the retro-orbital plexus using heparinized, sterile glass capillaries under diethyl ether anesthesia. The blood was then cool-centrifuged for 10 minutes at 3000rpm, separating the sera into aliquots and storing them at -80°C until biochemical measurements were performed. Following the collection of blood, the animals were quickly decapitated, and their livers were removed. Each liver portion was then washed in saline, dried, rolled in aluminum foil, and stored at -80°C for biochemical analysis and DNA fragmentation; a second portion of the liver was immersed in a formalin-saline (10%) buffer for microscopic inspection and histopathological processing.

6. Tissue homogenization

The liver specimen was homogenized in ice-cold phosphate buffer (50mM, pH 7.4) to produce a 10% homogenate (w/v). The nuclear and mitochondrial fractions were extracted from the homogenate by centrifuging it for 20 minutes at 5000rpm. The supernatant was then separated into aliquots and kept at -80°C until the biochemical measurements were made.

7. Biochemical determinations

Serum total protein and albumin levels were measured using reagent kits from DiaSys Diagnostic System GmbH, Germany; serum aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) activities were determined spectrophotometrically using reagent kits from Human Gesell Schaft fur Biochemical und Diagnostic mbH, Germany. Reagent kits from Biodiagnostic, Giza, Egypt, were used to measure the hepatic concentrations of reduced glutathione (GSH), nitric oxide (NO), and superoxide dismutase (SOD) and catalase (CAT) activity. On the other hand, as stated by **Ruiz-Larrea *et al*. (1994)**, the amount of malondialdehyde (MDA) was measured chemically.

8. Pro-inflammatory cytokines, and tumor markers

The ELISA technique (Dynatech Microplate Reader Model MR 5000) was used to measure the concentrations of serum tumor necrosis factor alpha (TNF-α), interlukin-1beta (IL-1β), interlukin-4 (IL-4), interlukin-6 (IL-6), interlukin-10 (IL-10), and alpha fetoprotein (AFP). Reagent kits were obtained from SinoGeneClon Biotech Co., Ltd., No. 9 BoYuan Road, YuHang District 311112, Hang Zhou, China.

9. DNA fragmentation percentage

By centrifuging the cleaved DNA from the intact chromatin and quantifying the amount of DNA in the supernatant and pellet using the diphenylamine test in accordance with the quantitative approach used to grade the DNA damage, the percentage of DNA fragmentation was ascertained **(Perandones *et al.*, 1993)**. The ratio of DNA in the supernatant to total DNA in the supernatant and pellet is known as the degree of DNA fragmentation. The following equation was used to determine the proportion of fragmented DNA based on the absorbance reading at 578nm:

$$\text{DNA fragmentation \%} = \frac{\text{A supernatant}}{\text{A supernatant} + \text{A pellet}}$$

10. Histopathology

After sacrificing, fresh liver specimens from the rats in different study groups were quickly removed according to the assigned schedule and fixed in 10% neutral buffered formalin solution. Following fixation, the tissue specimens were routinely processed for conventional histopathological examination. Sections of 5µm thickness were cut and stained with hematoxylin and eosin (H&E) stain **(Bancroft *et al.*, 1982)** for examination under a light microscope (Olympus CX31, Japan) and photographed using a digital camera (Toup View, LCMos10000KPA, China) in the Photomicrograph Lab of the Pathology and Clinical Pathology Department, Faculty of Veterinary Medicine, Assiut University. Hepatic histopathological lesions were graded on a scale of 0 to 4 according to methods adapted from **Richardson *et al.* (2010)**. The grading process involved examining the liver slides under the microscope to identify a range of lesions, such as coagulative necrosis in the hepatocytes and vascular changes.

11. Statistical analysis

According to **Steel and Torrie (1980)**, the one way analysis of variance (ANOVA) was used for multiple comparisons between means, and post hock (Tukey) was applied at $P \geq 0.05$. Statistical analysis system (SAS) computer software was used for this; copyright (c) 1998 SAS Institute Inc., Cary, NC, USA.

RESULTS

1. HPLC analysis of the sea anemone

HPLC analysis was used in SE to identify the 16 phenolic chemicals. It was discovered that the compounds have substantial concentrations of chlorogenic acid and gallic acid (Fig. 1 & Table 1).

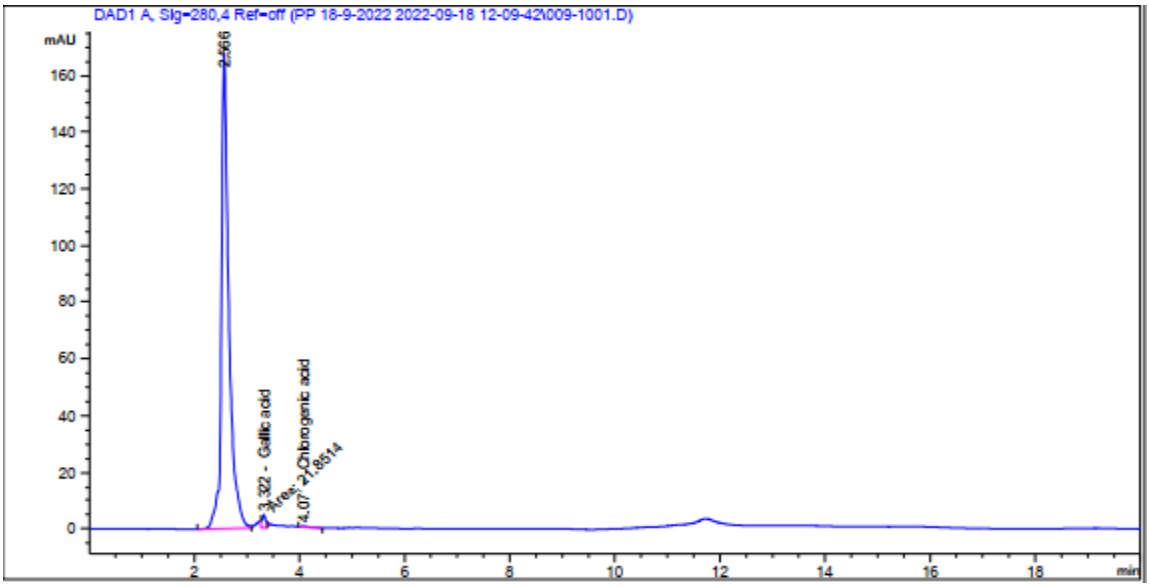


Fig. 1. HPLC analysis of phenolic constituents of the sea anemone extract

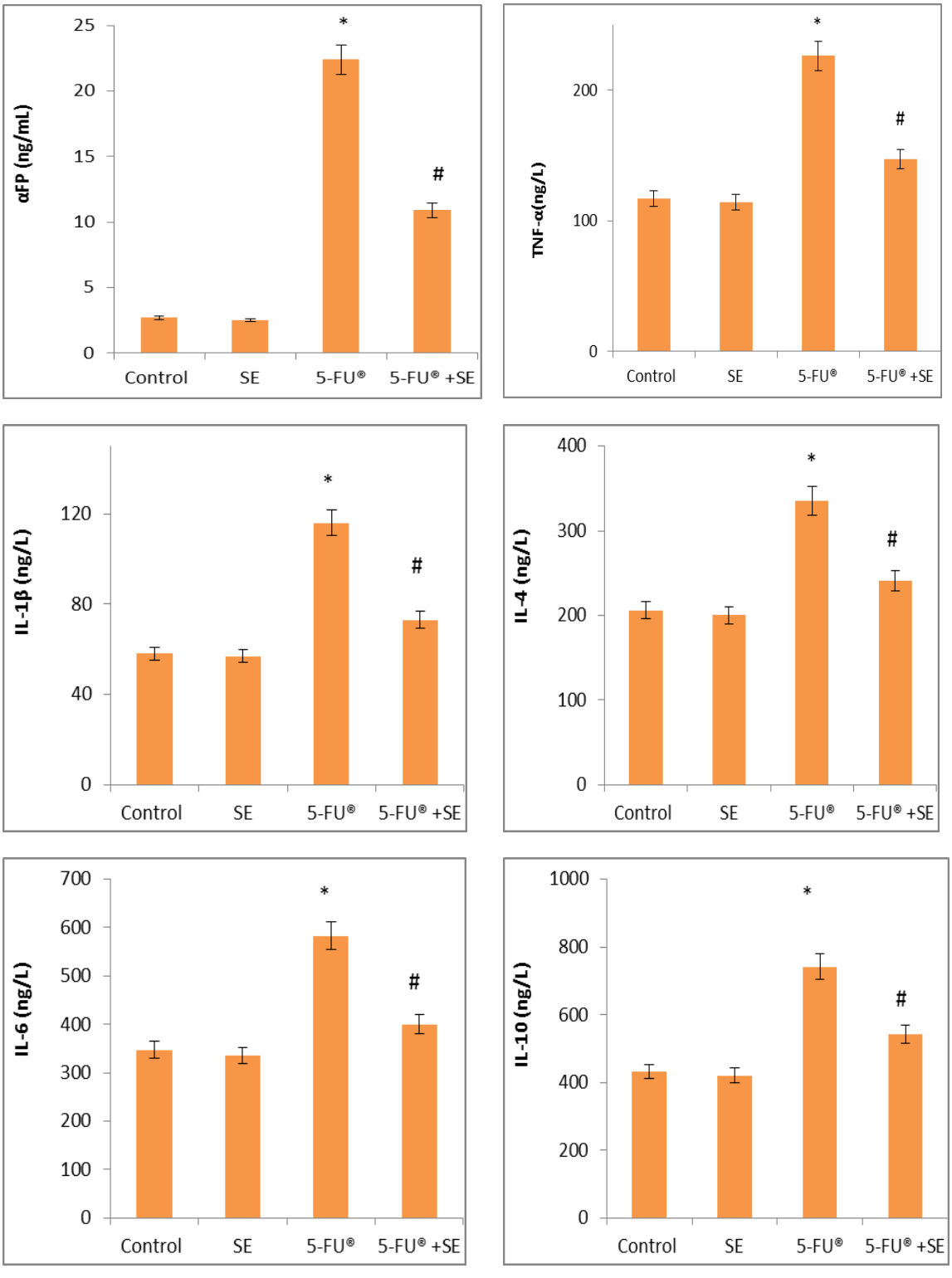
Table 1. Phenolic constituents of the extract of the sea anemone extract using HPLC analysis

	Area	Concentration (µg/ml = µg/ 6.8mg)	Concentration (µg/g)
Gallic acid	21.85	1.70	218.07
Chlorogenic acid	3.19	0.49	62.72
Catechin	0.00	0.00	0.00
Methyl gallate	0.00	0.00	0.00
Coffeic acid	0.00	0.00	0.00
Syringic acid	0.00	0.00	0.00
Pyro catechol	0.00	0.00	0.00
Rutin	0.00	0.00	0.00
Ellagic acid	0.00	0.00	0.00
Coumaric acid	0.00	0.00	0.00
Vanillin	0.00	0.00	0.00
Ferulic acid	0.00	0.00	0.00
Naringenin	0.00	0.00	0.00
Daidzein	0.00	0.00	0.00
Querectin	0.00	0.00	0.00
Cinnamic acid	0.00	0.00	0.00

2. Effect of the sea anemone extract on pro-inflammatory cytokines and DNA fragmentation

The results obtained demonstrated a significant increase in TNF-α, IL1β, IL-4, IL-6, IL-10, AFP, and hepatic DNA fragmentation level after 5-Fluorouracil® intoxication, as compared to the control group. Interestingly, when compared to rats that were 5-Fluorouracil®-intoxicated, the administration of SE to rats that were not intoxicated resulted in a significant decrease in the measured inflammatory cytokines (TNF-α, IL1β,

IL-4, IL-6, and IL-10); tumor marker (AFP); and hepatic DNA fragmentation to values were comparable to those of the normal control group (Fig. 2).



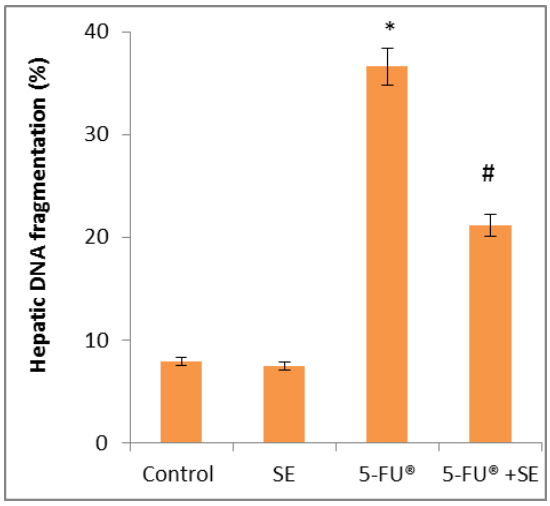


Fig. 2. Serum TNF-α, IL1β, IL-4, IL-6, IL-10 and α-FP levels as well as DNA Fragmentation of control, 5-Fluorouracil® -intoxicated and NE-treated male albino rats. * is significantly different from control group, while # is significantly different from 5-Fluorouracil® -intoxicated group ($P \leq 0.05$). SE (sea anemone extract); 5-FU; 5-Fluorouracil®.

3. Effect of the sea anemone extract on liver function

Table (2) presents data indicating that the administration of SE alone to rats did not cause any disruption in the activity of serum ASAT, ALAT, ALP, GGT, and bilirubin. However, when 5-Fluorouracil®-intoxicated rats were compared to the corresponding values of the control group, the activity of these parameters were significantly elevated. Positively, the 5-Fluorouracil®-induced declines in the specified parameters were considerably reduced by co-ingesting NE in accordance with the injection.

Table 2. Markers of liver function of control, 5-Fluorouracil®-intoxicated and SE-treated animals

	Control	SE	5-FU®	5-FU®+ SE
ALAT (U/L)	34.4±8.1	36.7±4.8	89.3±9.2*	49.5±3.0#
ASAT (U/L)	39.9±7.4	41.4±6.0	108.8±7.3*	60.9±3.1#
GGT (U/L)	49.2±5.8	49.3±2.2	102±8.08*	82.2±6.1#
ALP (U/L)	91.5±12.5	89.1±12.2	197.3±15.0*	146.6±11.1#
Albumin (g/dl)	4.1±0.17	4.3±0.32	2.9±0.8*	3.5±0.8#
Total protein (g/dl)	8.3±0.17	8.4±0.25	6.0±0.3*	7.5±0.2#
Bilirubin total (mg/dl)	0.32±0.02	0.30±0.03	1.24±0.02*	0.72±0.07#
Bilirubin direct (mg/dl)	0.059±0.03	0.056±0.006	0.24±0.005*	0.14±0.015#

Data are presented as mean ±SEM. Data were subjected to one way ANOVA followed by post hoc (Tukey) test at $P \leq 0.05$. * is significantly different from control group, while # is significantly different from 5-Fluorouracil®; SE (sea anemone extract); 5-FU; 5-Fluorouracil®.

Similarly, Table (2) demonstrates that, in comparison to the control group, there was a considerable drop in serum total protein and albumin levels following 5-Fluorouracil® poisoning. It's interesting to note that, in contrast to rats administered 5-Fluorouracil® injection, animals administered SE significantly increased serum total proteins and albumin levels, almost reached normal levels.

4. Effect of the sea anemone extract on anti-oxidative

Table (3) demonstrates that, when compared to the control group, rats intoxicated with 5-Fluorouracil® showed a considerable decrease in GSH, SOD, and CAT values together with a significant rise in hepatic MDA and NO levels. In contrast to the 5-Fluorouracil® group, treatment of animals with SE in addition to injection demonstrated a noteworthy restoration of GSH, SOD, and CAT values, as well as a considerable drop in hepatic MDA and NO levels.

Table 3. Hepatic values of malondialdehyde (MDA), nitric oxide (NO), reduced glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) of control, 5-Fluorouracil®-intoxicated and SE -treated male albino rats

	Control	SE	5-FU®	5-FU®+ SE
MDA (µmol/g tissue)	10.7±2.1	10.5±1.9	21.5±4.6*	14.5±2.5#
NO (µmol/g tissue)	22.4±4.0	21.7±1.3	37.5±3.4*	25.0±2.4#
GSH (nmol/g tissue)	125.9±3.8	134.3±5.3	88.3±2.8*	129.0±9.8#
SOD (U/g tissue)	872±125	868±107	327±47*	649±113#
CAT (U/g tissue)	31.7±5.5	34.8±4.11	16.0±2.03*	19.1±1.8#

Data are presented as mean ±SEM. Data were subjected to one way ANOVA followed by post hoc (Tukey) test at $P \leq 0.05$. * is significantly different from control group, while # is significantly different from 5-Fluorouracil®; SE (sea anemone extract); 5-FU; 5-Fluorouracil®.

5. Histopathological observations

Microscopic examination of the control hepatic sections revealed a normal hepatic histological appearance (Fig. 3A). The sea anemone extract-treated group displayed a slight hepatic sinusoidal dilatation (Fig. 3B). Focal areas of coagulative necrosis of hepatocytes associated with vascular changes were frequently observed in the liver sections of 5-Fluorouracil®-treated rats. The vascular changes were seen in the form of congestion of central veins, blood sinusoids (Fig. 3C) and portal blood vessels. Infiltration of the portal areas with inflammatory cells was also detected (Fig. 3D). In the sea anemone extract and 5-Fluorouracil®-treated group, just congestion of the sinusoids and central veins were noticed in some hepatic lobules (Fig. 3E). Grading of the histopathological hepatic lesions is shown in Fig. (3F). A significant decline in coagulative necrosis of hepatocytes as well as congestion of central veins, hepatic sinusoids and portal vessels was seen in the sea anemone extract and 5-Fluorouracil®-treated group in comparison with the 5-Fluorouracil®-treated group. A non-significant

difference was observed between the sea anemone extract-treated group and the control group.

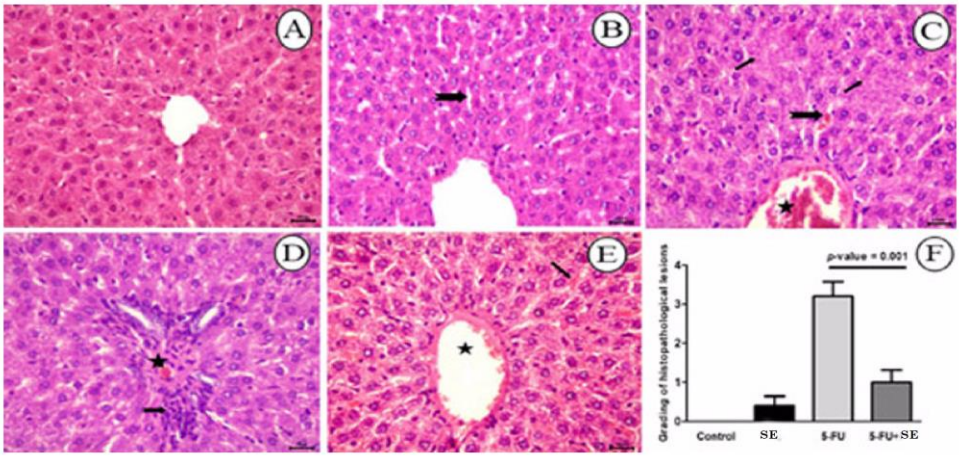


Fig. 3. Histopathological hepatic lesions; control group **(A)** showing normal histologic appearance of hepatic tissue. Sea anemone extract-treated group **(B)** showing dilated hepatic sinusoids (notched arrow). 5-Fluorouracil®-treated group **(C)** showing focal areas of hepatocytes coagulative necrosis (arrows), congestion of central vein (star) and sinusoids (notched arrow), **(D)** portal infiltration with inflammatory cells (notched arrow) and congested portal blood vessel (star). Sea anemone extract and 5-Fluorouracil®-treated group **(E)** showing slight congestion of central vein (star) and sinusoids (arrow). H&E. bar = 20. **(F)** Grading of histopathological hepatic lesions in experimental groups (n=5). Significance was observed between the 5-Fluorouracil-treated group and the sea anemone extract extract and 5-Fluorouracil-treated group. Significance was detected at $p < 0.05$. SE; sea anemone extract, 5-FU; 5-Fluorouracil®

DISCUSSION

5-FU is a common drug that has a chemotherapeutic effect. However, prior research has shown that using 5-FU can have certain negative effects **(Gelen *et al.*, 2018)**. Hepatotoxic consequences are among these negative effects. Various natural substances have been used in multiple research to mitigate the negative effects of such drugs on tissues. SE is one of these substances; it is claimed to have antioxidant and anti-inflammatory qualities. Thus, in this work, we examined how SE affected oxidative stress, inflammation, apoptosis, and tissue damage in hepatotoxicity resulting from 5-FU.

The findings acquired in this experiment demonstrated that elevated serum levels of ASAT, ALP, GGT, and bilirubin, along with reduced levels of albumin and protein, are unmistakable markers of 5-FU-induced hepatotoxicity. These findings are consistent with a recent study that found increased liver markers in the serum of rats given 5-FU **(Abd Elaty *et al.*, 2023; da Silva *et al.*, 2023)**. The current investigation found that the endothelium lining of the liver and its biological membranes were harmed by an excessive oxidative production and the buildup of oxidation products in the liver.

Elevated blood concentrations of ALAT, ASAT, GGT, and ALP were likely caused by liver injury. ALAT, ASAT, GGT, and ALP are considered to be the most significant biological indicators of cellular damage and toxicity **(Stockham & Scott, 2013)**. In other investigations, a notable increase in serum ASAT, ALAT, GGT, and ALP activity has been utilized as a marker of acute liver injury (25). In tandem with administration sea anemone (SE) demonstrated a hepatoprotective impact by drastically lowering elevated levels of ALP, GGT, ASAT, and ALAT to almost control levels. Using several hepatotoxic models, the hepatoprotective impact of SE on liver enzymes was demonstrated. Amines, proteins, and peptides are typically found among the chemical constituents of the sea anemone extract **(Mazzi Esquinca *et al*., 2023)**.

Essential markers for evaluating the ability to withstand oxidation are the activity of the enzymes SOD, GSH, and CAT. This study found that 5-FU reduced the activity of the SOD, GSH, and CAT enzymes, indicating a potential harm to the liver's antioxidant capability. Lipid peroxidation produces MDA, which is a useful indicator of oxidative damage. In biology, NO is a highly reactive free radical. The results of this study indicate that 5-FU exacerbates an oxidative stress in the liver by raising MDA and NO levels. Furthermore, cells experience an uncontrollable increase in ROS, which can cause DNA damage to accumulate and accelerate the apoptotic process **(Barzilai & Yamamoto, 2004; Garinis *et al*., 2008)**. DNA damage is caused by oxidative stress, which sets off the DNA damage response (DDR). It's interesting to note that SE was able to prevent 5-FU since it significantly increased radical scavenging activity, which in turn stopped the advancement of oxidative stress. In this approach, SE stimulation of SOD and CAT serves in protecting the cell from oxidative stress. Restoration of GSH has a multifunctional role in antioxidant defense, as both a direct scavenger of free radicals and as a co-substrate for peroxide detoxification by glutathione peroxidases **(Berger *et al*., 2022)**.

Throughout the current experiment, the administration of 5-FU resulted in a considerable increase in serum levels of the pro-inflammatory cytokines TNF-α, IL-β1, IL-4, IL-6, IL-10 and tumor biomarker AFP. These findings are consistent with those of previous research **(da Silva *et al*., 2023)**. Research has demonstrated that the liver is more vulnerable to inflammatory responses when oxidative stress and steatosis are present **(Hardy *et al*., 2016)**. This was supported by our findings, which showed that the livers of the treated rats had higher levels of the inflammatory process enzyme indicators MDA and NO. In addition, rats given 5-FU showed elevated serum levels of the tumor biomarker AFP and pro-inflammatory cytokines TNF-α, IL-β1, IL-4, IL-6, and IL-10.

The enlargement of sinusoid capillaries and other histological alterations in the liver tissue may be brought on by oxidative stress and inflammation (**Brancatelli *et al*., 2018)**. The study revealed a noteworthy rise in the width of the sinusoid capillaries in the rats administered 5-FU. The enlarged nuclei and superficial regions of the hepatocytes following 5-FU therapy was another histological change. The nuclei and superficial area

are growing, which suggests hepatocyte hypertrophy. According to **Neufeld and Edgar (1998)**, the rate of division of a cell is correlated with its growth rate. Consequently, the cell cycle block may be connected to cell hypertrophy **(Neufeld & Edgar, 1998)**; this results from 5-FU's activity **(Wigle *et al*., 2019)**. TNF-α, IL-1β, IL-4, IL-6, and IL-10 levels in blood serum were all lower after supplementing with NE, which inhibited 5-FU-induced inflammation and supported biochemical and histological findings. These results demonstrated that the sea anemone-mediated inhibition of inflammation is essential to their hepatoprotective benefits.

CONCLUSION

In summary, our findings show that the inherited anti-inflammatory, hepatoprotective, and antioxidant properties of sea anemone extract considerably mitigated 5-Fluorouracil®-induced hepatotoxicity. SE may be useful in treating a variety of liver-related illnesses and aiding in the long-term 5-Fluorouracil® treatment plan.

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