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The Potential Protective Effects of Brown Algae (*Sargassum subrepandum*) Powder on Benzo[*A*]Pyrene-Induced Hepatic and Renal Dysfunction in Rats

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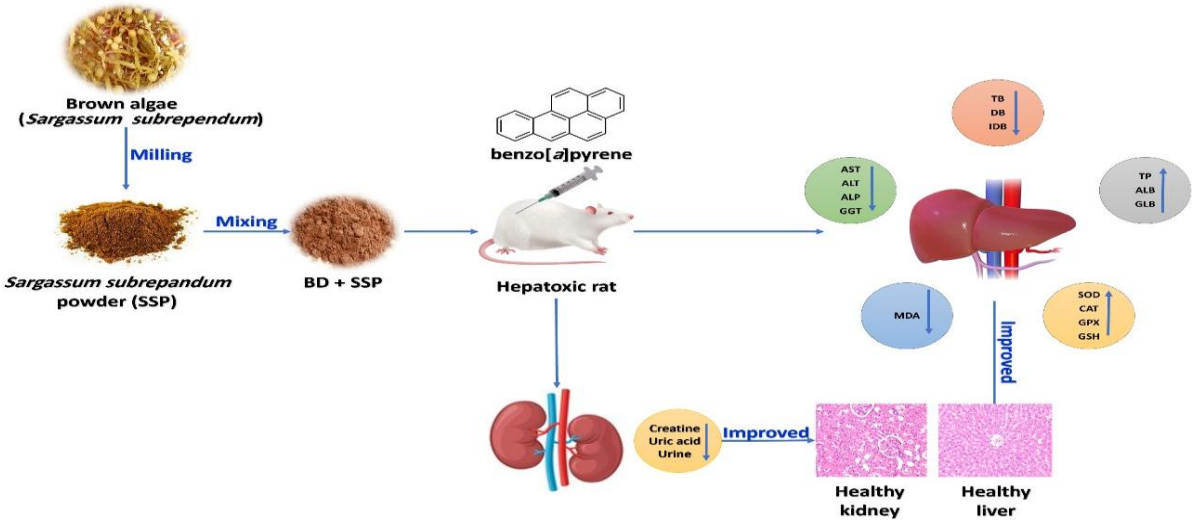
ABSTRACT

Benzo[*a*]pyrene (B[*a*]P) is a primary representative of polycyclic aromatic hydrocarbons (PAHs) that are produced during various food preparation and processing methods, such as baking, frying, grilling, and smoking. Exposure to B[*a*]P has been linked to liver toxicity and carcinogenic effects across all vertebrate species. This study aims to explore the potential protective effects of brown algae (*Sargassum subrepandum*) powder on benzo[*a*]pyrene-induced hepatic and renal dysfunction in rats. Thirty male albino rats were classified into two main groups, the first group (G1, 6 rats, as a negative control group) was fed the basal diet (BD) and the second main group (24 rats), challenged with B[*a*]P, was assigned to four groups of 6 rats per each as follow: group 2 (G2) acted as a model control of hepatotoxic rats, while groups (3-5) received *Sargassum subrepandum* powder (SSP) at concentrations of 1.5, 3.0 and 6 g/100g diet for 28 days each, respectively. B[*a*]P exposure significantly ($p \leq 0.05$) increased liver enzymes activities [AST (72.27%), ALT (95.94%), ALP (243.01%) and GGT (670.08%)], renal function indicators [serum urea, (231.88%), uric acid (170.05%) and creatinine (79.36%)], and MDA (2984.37%) accompanied by severe histopathological changes in liver and kidney tissues comparing to the normal control group. Also, a significant ($p \leq 0.05$) deficiency in antioxidant enzymes [SOD (-78.14%), CAT (-97.35%) and GPX

(-89.82%)], GSH (-86.98%), and immunoprotenis [albumen (-31.15%) and globulin (-30.62%)] were recorded. Treatment with SSP for 24 days exhibited a significant ($p \leq 0.05$) improvement in all of these parameters and the histoarchitecture of the liver and kidneys by different rats. The improvement in all assessed parameters demonstrated a dose-dependent response to the SSP intervention. In conclusion, the present results from this study indicate that treatment with SSP at the evaluated concentrations effectively mitigated the biochemical and histological injuries to the liver and kidneys induced by B[*a*]P, highlighting the potential of this intervention.

Keywords: liver enzymes, renal functions, bilirubin, antioxidant enzymes, plasma proteins, histopathology.



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INTRODUCTION

Brown algae (Family: *Phaeophyceae*) encompasses a diverse array of predominantly marine multicellular algae, inclusive of various species of seaweed, primarily found in the colder waters of the Northern Hemisphere (Hoek *et al*., 1995). It lives in coral reefs, although they are considered waste by coastal communities (Coyer *et al*., 2001). Most brown algae are inclusive by the presence of the pigment fucoxanthin, which imparts their characteristic greenish-brown coloration, given their name by Batista-Gonzalez *et al*. (2020). Worldwide, over two thousand species of brown algae are known, and almost all of them are of substantial commercial use due to their having been subjects of extensive research in their own right (Mann and Martin, 2002). Among these genera comes the *Sargassum* genus which contains a huge number of species. Members of the *Sargassum* genus are recognized as valuable sources of various nutrients, including lipids, vitamins, minerals, proteins, essential fatty acids, and amino acids, along with active secondary metabolites (Hussain *et al.*, 2016; El-Gamal, 2020; Elhassaneen *et al.*, 2020 and Abd Elalal *et al*., 2021). In this context, such organisms contain a large amount of minerals such as iodine, iron, calcium, copper and magnesium (Abd Elalal *et al*., 2021). Also, Eckel *et al*. (2010) pointed out that brown algae possess a substantial percentage of iodine, so a quarter cup of algae suffices the human need for iodine for three days. For the active secondary metabolites, polysaccharides are major components in brown algae, including the *Sargassum* genus and inclusive cellulose, alginates, and sulfated polysaccharides like laminarans and fucoidans (Abd Elalal *et al*., 2021). Such compounds also include free mannitol, alkaloids, peptides, polyphenols, fatty compounds, and various pigments (Chapman *et al*., 1959 and El-Gamal, 2020). Polyphenols are a class of polymers characterized by phloroglucinol as their fundamental unit, commonly found in various organisms, and play a vital role in the structure of their cell walls (Elhassaneen *et al*., 2020). Also, brown algae comprise a variety of secondary metabolites, including alkaloids, glycosides, tannins, steroids, fucoidans, phlorotannins, meroterpenoids, laminarin, sterols, and glycolipids, which have been identified in members of the *Sargassum* genus (Hossain *et al*., 2003 and Abd Elalal *et al*., 2021). All of these previous studies and others have confirmed the possibility of benefiting from brown algae in many important life matters, including nutritional and therapeutic applications. For example, *Sargassum* genus is commonly utilized in dried form as a condiment and soup base, or consumed fresh in rolls, stews, salads, and alongside rice. Thus, it is hypothesized that the overall composition of certain traditional Asian diets may play a role in the lower incidence of cancer, especially breast cancer (Kanke *et al*., 1996 and Ozougwu, 2017). Also, a wide range of pharmacological properties of the *Sargassum* genus, extracts or isolated pure components, have been recognized including anticancer, anti-inflammatory, anti-fungal, anti-bacterial, anti-viral, anti-coagulant, antioxidant, hypoglycemic, hepatoprotective and neuroprotective activates (Abd Elalal *et al*., 2021 and Ataa *et al*., 2021**).** With this context, Funahashi *et al.* (2001) reported that the consumption of brown algae is associated with variations in breast cancer levels. The same observation was recorded by Kanke *et al*. (1996) who found that, as the result of brown algae consumption, the Japanese population exhibits a nine fold-lower incidence of breast cancer, with even lower rates observed in the Korean population when compared to Western populations. Also, Ajami (2022) attributed the relative longevity and health of the Okinawan Japanese population, in part, to their dietary intake of algae, as highlighted in their studies. Furthermore, several authors indicated that intervention with *Sargassum* genus reduced complications of diabetes, obesity and osteoporosis in rats (Fayez, 2016; El-Gamal, 2020; Elhassaneen *et al*., 2020 and Gad Alla, 2023). Finally, Elhssaneen *et al*. (2023a, b) and (2024) found that *Sargassum* genus powder consumption inhibits benzo[a]hepatotoxicity due to its high contain of several classes of active secondary metabolites and their several biological activities including antioxidant activities.

The liver is an essential organ in the human body which makes up about 2% of the body weight of an adult. It carries out many tasks that, among other things, support immunity, digestion, detoxification, metabolism, and vitamin storage (Elhassaneen, 1996; Kakkar *et al*., 1998 and Elhassaneen *et al*., 2023a, b). Because the liver receives blood from both the portal vein (about 75%) and the hepatic artery (about 25%), it is a special organ. Due to its close ties to almost all bodily systems, it is vulnerable to a wide range of diseases (Farvin & Jacobsen, 2013 and Elhassaneen *et al*., 2021b, c). The principal role of this system is to control the flow and safety of chemicals absorbed from the digestive tract before their being distributed into the systemic circulatory system. The liver's critical role is highlighted by the possibility that complete hepatic failure could result in death in a matter of minutes (Ozougwu, 2017). Liver dialysis can be utilized temporarily, but at this point, there is no long-term solution to replace the liver's essential role in life support. For that, the liver is essential for survival, and its diseases impose significant economic, humanistic, and clinical burdens worldwide.

It is well known that when the right precursors are available, cooking can produce harmful chemicals in food (Elhassaneen and Tawfik, 1998). Within these compounds, polycyclic aromatic hydrocarbons (PAHs) resulting from incomplete combustion are present in various foods, including those that are charcoal-broiled or smoked (Mannervik, 1985). Benzo[*a*]pyrene (B[*a*]P), a member of the PAH family, is found in coal tar and has the chemical formula $C_{20}H_{12}$. This compound, a type of benzo[*a*]pyrene, is formed by the fusion of a benzene ring with pyrene and is generated through incomplete combustion at temperatures ranging from 300 to 600°C (Elhassaneen, 1996). Such as reported by Loomis *et al.* (2014), B[*a*]P metabolites are both mutagenic and highly carcinogenic, classifying it as a Group 1 carcinogen. Also, several authors documented that B[*a*]P exhibits toxic, mutagenic, and/or carcinogenic properties based on extensive in vivo and in vitro experiments (Hawkins *et al*., 1990; Elhassaneen, 1996; Hassan *et al*., 1996; Elhassaneen *et al*., 2016b; Badawy, 2017; Mahran *et al*., 2018 and Mahran & Elhassaneen, 2023). Since the 1970s, numerous studies have established connections between B[*a*]P exposure and various cancers (Ozougwu, 2017). Furthermore, exposure to B[*a*]P is linked to the development of liver toxicity and carcinogenicity across all vertebrate species (Hawkins *et al*., 1990; Elhassaneen, 1996; 2002 and Elhassaneen & Mahran, 2024). It is understood that the toxic and carcinogenic effects of B[*a*]P are associated with its cellular biotransformation into several reactive intermediates/metabolites, such as arene oxides, quinones, phenols, epoxides, and dihydrodiols. These metabolites subsequently interact covalently with DNA, leading to the formation of adducts. Also, B[*a*]P induced a cytotoxic effect through the ability of these reactive metabolites to cause oxidative stress in different cell membranes, causing major damage to their vital functions (Weinstein, 1978; Pagana & Pagana, 1997; Elhassaneen, 1996; Kaarthik *et al*., 2012; Aly *et al.*, 2017; Cao *et al*., 2020 and Mahran & Elhassaneen, 2023).

Over the decades, many medical preparations have been discovered to treat liver disorders caused by environmental and food pollutants, such as B[*a*]P. Now, many of these preparations often cause major complications in the body that may be difficult to deal with, in addition to the bad economic aspect caused by these medical preparations due to their high coast, which makes them unavailable to the general public, especially the poor (Tandon *et al*., 2022). With this respect, medications that are primarily metabolized by the liver can have their clearance significantly impaired in individuals with liver disease, leading to an accumulation of these drugs in the body (Shargel *et al*., 2016). Thus, certain prescription medications may pose a risk of liver damage and are generally not advised for patients with pre-existing liver conditions. Recently, researchers in many research centers and universities have turned their attention to using natural preparations resulting from plant parts that contain active secondary metabolites to treat liver diseases (El-Beshlawy *et al*., 2003.; Ibrahim *et al*., 2004; Elhassaneen *et al*., 2012; 2016 a, b; 2021 c, b; 2023 a, b; Elhassaneen & Abd Elhad, 2014; Elhassaneen & Kamal, 2014; Sayed Ahmed *et al*., 2016; Badawy, 2017; 2021; Mahran *et al*., 2018 and Mahran & Elhassaneen, 2023). Numerous of these studies have proven the effectiveness of these preparations in this attention additionally their non-harmful side effects and low cost. The results of these studies encouraged the search for new plant parts that are effective and sustainable for this purpose. Thus, this current study is to evaluate the potential impact of intervention with brown algae (*Sargassum subrepandum*) powder on benzo[*a*]pyrene-induced hepatic and renal dysfunction in rats.

MATERIAL AND METHODS

Brown algae

Brown algae (*Sargassum subrependum*) were obtained from the marine coasts of the Mediterranean in Alex., Egypt. After being drained of excess water, the samples were validated by personnel at the Faculty of Agriculture, Alex. Uni., Egypt.

Chemicals and Kits

B[*a*]P was obtained from Sigma Chemical CO., St. Louis, MO, USA. All other chemicals (Except as otherwise stated), solvent, buffer, casein, vitamins, minerals, cellulose, chloride sodium and tween were obtained from El-Gomhoriya Company for Trading Drugs and Medical Instruments, Cairo, Egy. Kit's assays for Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total Protein, albumin (Alb), globulin, Creatinine, urea, uric acid, and malondialdehyde (MDA) were purchased from BIODIAGNOSTIC, Dokki, Giza, Egy. Reduced glutathione (GSH) was assayed by the kits provided by My Bio Source, Inc., San Diego, CA, USA.

Basal Diet (BD)

The BD was prepared using the formula outlined by Reeves *et al*. (1993), which includes the following components: 10% protein, 10% corn oil, 1% vitamin mixture, 4% mineral mixture, 0.2% choline chloride, 0.3% methionine, and 5% cellulose, with corn starch 69.5% making up the remaining. The formulations for the vitamin and mineral mixtures were also based on the same reference.

Animals and maintenance

Thirty normal adult male Sprague Dawley albino rats, weighing 150±170 g each, were obtained from Helwan Station, Ministry of Health and Population, Helwan, Cairo, Egypt. The rats were housed in stainless steel cages maintained at 25±2°C, 59±3.5% relative humidity, and a 12/12-hour light/dark cycle. For acclimatization, all rats were fed a basal diet (BD) for two weeks before the experiment commenced.

Methods

Preparation of brown algae powder

After arriving at the lab, *Sargassum subrepandum* samples powder were prepared according to Gharib *et al*. (2022). In summary, a sample of fresh algae was manually cleaned and sorted before being dried in a hot air oven (Horizontal Forced Air Drier, Proctor and Schwartz Inc., Philadelphia, PA) at 60°C until the moisture content of the final product reached approximately 7%. The dried algae were then ground into a fine powder using a high-speed mixer (Moulinex Egy., Al-Araby Co., Egy.), and the material that passed through an 80-mesh sieve was collected for further use. To minimize oxidation of the contents, the powder samples were stored in dark, airtight glass jars in a cool, dry environment until needed for analysis.

Biological experiments

Induction of liver injury

Hepatotoxicity in healthy male albino rats was induced by B[*a*]P injected intraperitoneally with a single dose of B[*a*]P (125 mg/kg/b. wt. in corn oil) and used for the feeding protocol experiment after two weeks such as described by Shahid *et al*. (2016).

Experimental design

All biological experiments were conducted in the biology unit at the Faculty of Home Economics, Menoufia Uni., Shebin El-Kom, Egy., following the guidelines set forth by the Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council (NRC, 1996). Following a one-week acclimatization period, a total of 30 rats were divided into two main groups. The first group (G1), consisting of 6 rats, served as the negative control group, continuing to receive the basal diet (BD) and administered corn oil intraperitoneally at a dosage of 10 ml/kg/b.wt on the seventh day only and the second main group (24 rats), challenged with B[*a*]P, was assigned to four groups of 6 rats per each as follow: group 2 (G2) acted as a model control of hepatotoxic rats, while groups (3-5) received *Sargassum subrepandum* powder at concentrations of (1.5, 3.0 and 6 g/100g diet) for 28 days each, respectively. *Sargassum subrepandum* powder concentrations were selected for the study based on several previous studies (Fayez, 2016; El-Gamal, 2020; Abdelrahman, 2022 and Elhassaneen *et al*., 2023 a,b).

Blood sampling

After the experimental period (4 weeks), the rats were fasted overnight prior to euthanasia. Samples of blood were collected from each rat via the abdominal aorta, and the rats were sacrificed under ether anesthesia. The blood samples were placed in clean, dry centrifuge tubes and allowed to clot at room temperature (37°C) for 28 minutes. Following this, the samples were centrifuged for 10 minutes at 3000 rpm to separate the serum, following the method described by Stroev and Makarova (1989). The serum was carefully aspirated, transferred into clean storage tubes, and stored frozen at -20°C until further analysis.

Organs sampling

The liver and kidneys were removed from rats by careful dissection, and the suspended blood was removed immediately after the animals were slaughtered. The organs were washed with cold saline, dried between two papers of filter, weighed, and preserved in a 10% solution of formalin for histological examination, according to methods described by Drury and Wallington (1980). Relative organ weight (ROW) was calculated according to Fielding (1998) as follows: Fresh organ weight/Final weight x100.

Biological Evaluation

On the diet taken, records were kept daily for 28 days while the body weight was weighed every week. The parameters for body weight gain (BWG %), FI food intake, and FER food efficiency ratio were assessed following the methodology outlined by Chapman (2012). The calculations were performed using the formulas: BWG (%) = [(Final weight – Initial weight)/Initial weight] × 100 and FER = grams of body weight gained (g over 28 days)/grams of feed consumed (g over 28 days).

Biochemical analysis

Liver function

Liver functions were determined using specific methods as follows: alkaline Phosphatases (ALP) pointed out by Tietz (1976), aspartate aminotransferase (AST), alanine aminotransferase (ALT) according to Henry *et al*. (1974), Gamma-Glutamyl Trans peptidase (GGT), according to Yound (1975), total Bilirubin (T.B) according to Vassault *et al*. (1999), direct Bilirubin (D.B) according to Vassault *et al*. (1999), and indirect bilirubin (ID. B) according to Kachmar and Moss (1976).

Kidney function

Serum levels of urea, creatinine, and uric acid were measured using the methods outlined by Rosner & Bolton (2006); Henry *et al*. (1974) and Schultz (1997).

Immunological functions

Serum total Protein (T.P), albumin (Alb) and globulin (G), were determined consistent by Tietz (1976); Raulf *et al*. (1985) and Lopes-Virella *et al*. (1977).

Redox status

Reduced glutathione (GSH) levels in serum samples were quantified calorimetrically following the procedure outlined by Sies (1997). (SOD) Superoxide dismutase, (CAT) catalase and (GPX) glutathione peroxidase, were determined in serum according to the method of Liu C *et al*. (2011); Erel (2005) and Goodsell & Olson (2000). The serum inclusive of malondialdehyde (MDA) was assessed using the thiobarbituric acid (TBA) method, as described by Buege and Aust (1978).

Histopathological Investigation

Small specimens of liver and kidney were obtained from all groups of experimental and fixed in 10% neutral buffered formalin. The samples were then dehydrated through increasing concentrations of ethanol (70%, 80%, and 90%), cleared in xylene, and embedded in paraffin. Sections with a thickness of 4-6 µm were prepared and stained with Hematoxylin and Eosin following the methodology described by Drury and Wallington (1980).

Statistical Analysis

By using the computerized COSTAT program employing one-way ANOVA, the data were statistically analyzed. The results are expressed as mean ± SD, and differences between treatments were considered.

RESULTS AND DISCUSSION

Effect of four weeks of intervention with *Sargassum subrependum* powder (SSP) on (BWG), (FER) and (FI) of hepatotoxic rats.

Data in Tables (1 and 2) point out the effect of *Sargassum subrependum* powder (SSP) on Body Weight Gain, Food Efficiency Ratio, Feed Intake and Weight Gain of hepatotoxic rats. With such data, it is possible to notice that the rats under B[*a*]P treatment showed a highly significant ($p \leq 0.05$) decrease in BWG (-31.72%), FI (-33.70%) and FER (-25.59%) in comparison with a control group. Nevertheless, the administration of SSP (1.5 to 6 g/100g diet) over 28 days period had a significant outcome ($p \leq 0.05$) with enhancement across all measured parameters. The increase in BWG, FI, and FER exhibited a dose-dependent relationship with SSP concentration. These effects of B[*a*]P in reduction of the BWG, FER and FI could be attributed to the oxidative stress and toxicity induced by exposure to such compound. As reported by Elhassaneen and Mahran (2024), exposure to B[*a*]P imposes an extra burden on vital organs, particularly the liver and kidneys, which have a crucial role in the metabolism and excretion of that compound to mitigate its harmful effects, potentially leading to inflammation and enlargement of these organs. These data are in line with Elhassaneen *et al*. (2018) and Mahran & Elhassaneen (2023) who reported that exposure to B[*a*]P in male albino rats resulted in a significant reduction in the animals' body weight in comparison to normal control rats. Conversely, feeding intervention with SSP in B[*a*]P-treated rats demonstrated a notable increase in BWG, FI and PER. Such data are similar to the study of Hassan *et al*. (1996) who reported that brown algae powder that was present in the feeding protocol improved the FER of rats with hepatotoxicity. Also, Farvin and Jacobsen (2013) showed that there was an increased weight gain in hepatotoxic rats treated with brown algae powder. Such as reviewed by Hamzawy *et al*. (2013) and El-Gamal (2020), the observed increases with (BWG), (FI), and (FER).

Table 1. Effect of four weeks of intervention with *Sargassum subrependum* powder (SPP) on (BWG), (FER) and (FI) of hepatotoxic rats

Groups	Food efficiency ratio (FER)	Feed intake (FI, g/day/rat)	Body weight gain (BWG, %)
G1 (Normal control)	1.012±0.004 [a]	11.76±0.52 [a]	0.089 ±0.007 [a]
G2 (Model control)	0.691±0.012 [d]	8.75±0.49 [d]	0.059 ±0.019 [b]
G3 (SSP, 1.5% of BD)	0.768±0.010 [d]	9.55±0.32 [c]	0.067 ±0.005 [b]
G4 (SSP, 3.0 % of BD)	0.861±0.008 [c]	10.22±0.60 [bc]	0.074 ±0.004 [ab]
G5 (SSP, 6.0% of BD)	0.981±0.022[b]	10.61±0.29 [b]	0.081 ±0.007[a]
LSD	0.140	3.461	0.784

Each value represents mean ± SD (n=6). Mean under the same column bearing different superscript letters are different significantly (p<0.05). Normal control, healthy rats without intervention; Model control, B[*a*]P injected rats without intervention; SSP, *Sargassum subrependum* powder; BD, basal diet; groups (G3, G4 and G5), B[*a*]P injected rats with SSP intervention; LSD is the least significant variation.

Table 2. Effect of four weeks' of intervention with *Sargassum subrependum* powder (SPP) on (BWG), (FER) and (FI) (as a percent of control) of hepatotoxic rats

Groups	BWG	FER	FI
G1 (Normal control)	------	-------	-------
G2 (Model control)	-31.72 ± 2.34	-25.59 ± 1.77	-33.70 ± 2.45
G3 (SSP, 1.5% of BD)	11.14 ± 0.98	9.14 ± 0.69	13.56 ± 0.93
G4 (SSP, 3.0 % of BD)	24.60 ± 1.09	16.80 ± 1.11	25.42 ± 2.17
G5 (SSP, 6.0% of BD)	41.96 ± 3.67	21.25 ± 2.06	37.28 ± 4.23

The guides of the groups of experimental are shown in Table1. The Percentage of change (%) for the model control group is calculated in comparison with the controls, while it is calculated for the SPP treated groups in comparison to the model controls. Food efficiency ratio (FER), Feed intake (FI), Body weight gain (BWG).

Following the intervention with brown algae powder can be attributed to its rich nutrient profile and the presence of bioactive compounds, which contribute to various biological activities. In a similar context, El Maaiden *et al*. (2019) found that an alginate complex present in brown algae increased body weight in rats with hepatotoxicity. Also, Fariman *et al*. (2016) showed that fucoidan, alginate, and laminarin present in brown algae affected and improved FER in rats with hepatotoxicity.

Effect of four weeks of intervention with *Sargassum subrependum* powder (SSP) on liver functions of hepatotoxic rats

The effect of four weeks of intervention with *Sargassum subrependum* powder (SSP) on liver functions of hepatotoxic rats is pointed out in Tables (3 and 4). Based on these data, it can be observed that the rats injected with B[*a*]P exhibited significantly ($p \leq 0.05$) elevated levels of AST (72.27%), ALT (95.94%) ALP (243.01%) and GGT (670.08%) in comparison to a normal group. The intervention with varying concentrations of SSP (1.5, 3.0, and 6 g/100g of diet) over four weeks period resulted in a significant ($p \leq 0.05$) reduction in the activities of these enzymes, at rates of -45.89% (for AST); -38.77% (for ALT), -67.61 % (for ALP), and -87.25% (for GGT) in comparison to normal control animals, correspondingly. The observed reductions in all of these parameters demonstrated a dose-dependent manner with the SSP concentrations. These data are in accordance with a lot of authors who discovered that B[*a*]P-induced liver damage in the model

Table 3. Effect of four weeks of intervention with *Sargassum subrependum* powder (SSP) on liver functions of hepatotoxic rats

Groups	Serum alanine aminotransferase activity ALT (U/L)	Serum Aspartate aminotransferase activity (AST, U/L)	Serum alkaline phosphatase ALP (U/L)	Gamma-glutamyl Transferase GGT (U/L)
G1 (Normal control)	63.42^{d}±6.166	125.6^{d}±8.241	123.32^{c}±15.249	2.44^{d}±0.594
G2 (Model control)	124.27^{a}±4.689	216.37^{a}±9.163	423^{a}±34.158	18.79^{a}±1.365
G3 (SSP, 1.5% of BD)	98.39^{b}±7.527	164.23^{b}±8.964	190.31^{b}±11.598	11.76^{b}±1.828
G4 (SSP, 3.0 % of BD)	91.7^{b}±6.201	141.42^{c}±5.885	132.65^{c}±4.442	6.14^{c}±0.924
G5 (SSP, 6.0% of BD)	76.08^{c}±5.644	117.06^{d}±11.763	137^{c}±17.469	2.395^{d}±0.467
LSD	7.748	10.117	23.048	0.982

The guides of the experimental groups are shown in Table1. Each value represents mean ± SD (*n*=6). Means in the same column with different superscript letters differ significantly ($p<0.05$). LSD represents the least significant variation.

Table 4. Effect of four weeks of intervention with *Sargassum subrependum* powder (SSP) on liver functions (as a percent of control) of hepatotoxic rats

Groups	Serum alanine aminotransferase activity ALT (U/L)	Serum Aspartate aminotransferase activity (AST, U/L)	Serum alkaline phosphatase ALP (U/L)	Gamma-glutamyl Transferase GGT (U/L)
G1 (Normal control)	------	-------	------	------
G2 (Model control)	95.94 ± 9.79	72.27 ± 5.78	243.01 ± 23.35	670.08 ± 20.45
G3 (SSP, 1.5% of BD)	-20.82 ± 1.55	-24.09 ± 2.87	-55.01 ± 5.32	-37.41 ± 3.78
G4 (SSP, 3.0 % of BD)	-26.21 ± 2.09	-34.64 ± 3.78	-68.64 ± 4.67	-67.32 ± 4.21
G5 (SSP, 6.0% of BD)	-38.77 ± 4.08	-45.89 ± 4.05	-67.61 ± 6.21	-87.25 ± 5.08

The guides of the groups of experimental are shown in Table1. The Percentage of change (%) for the model control group is calculated in comparison with the controls, while it is calculated for the SPP-treated groups in comparison to the model controls.

Animals commonly used in experimental studies regarding the protective effects of drugs, natural extracts, and functional foods related to liver disease (Elhassaneen *et al*., 1996 a,b; Kiruthiga *et al*., 2015; Fayez, 2016; Mahran *et al*., 2018; Shannon *et al.*, 2019; Mahran & Elhassaneen, 2023 and Elhassaneen & Mahran, 2024). The B[*a*]P liver damages are due to the cellular biotransformation of these compounds to several reactive intermediates/metabolites as phenols, arene oxides, dihydrodiols, quinones, and epoxides and the subsequent formation of compounds that covalently interact with nucleic acids to create adducts. Also, B[*a*]P induced a cytotoxic effect through the ability of these reactive metabolites to cause oxidative stress in different cell membranes, causing major damage to their vital functions (Weinstein, 1978; Pagana & Pagana, 1997; Harvey, 1985; Elhassaneen, 1996; 1999; 2004; Kaarthik *et al*., 2012; Elhassaneen & El-Badawy, 2013; Aly *et al*., 2017; Cao *et al*., 2020; Mahran & Elhassaneen, 2023 and Elhassaneen & Mahran, 2024). Data from the current study revealed that injection B[*a*]P resulted in significant hepatic cell damage, as evidenced by increased serum levels of AST, ALT, ALP, and GGT. Aminotransferases (ALT and AST) and ALP are typically found within cells, and their elevated presence in plasma indicates cellular injury, particularly in tissues rich in these enzymes (Pagana & Pagana, 1997; Sayed-Ahmed *et al*., 2020 and Elhassaneen *et al*., 2023 a, b). Additionally, GGT, which is located in the membranes of various tissues such as the kidneys, pancreas, spleen, bile duct, gallbladder, heart, seminal vesicles, and brain, plays a crucial role in the transfer of amino acids across cellular membranes, as well as in leukotriene and glutathione metabolism (Meister, 1974 and Raulf *et al*., 1985). GGT facilitates the transfer of the glutamyl moiety to various acceptor molecules, including certain L-amino acids, water, and peptides, thereby helping to maintain intracellular oxidative stress homeostasis. Thus, elevated activity of this enzyme in the serum is evidence that cells are exposed to oxidative stress.

The present data also declared that treatment with the SSP nominally reduced AST, ALT, ALP and GGT levels which demonstrates that it could be prevent liver cell damage. Such preventive roles could be attributed to the high content of some important bioactive constituents that have been determined in SSP with different biological activities including antioxidant activities. These findings are consistent with Kushnerova *et al*. (2010) who pointed out that plant polyphenols extracted from brown algae exhibit significant antioxidative properties, serving as effective and low-toxicity hepatoprotectors that target the primary mechanism behind toxic hepatitis, specifically by reducing lipid peroxidation. These compounds also enhance the detoxification and excretory functions of hepatocytes. Furthermore, Taskin *et al*. (2010) highlighted that brown algae are rich in unique polysaccharides that function as beneficial dietary fibers, helping to regulate energy intake, nutrient absorption, and overall metabolic homeostasis, as shown by the low activates of liver enzymes (AST, GGT and ALT). The same behavior was reported by many authors who found that treatment with polyphenols, flavonoids, laminarin and alginate from brown algae has antioxidant activates and hepatoprotective properties by decreasing ALP, AST, GGT and ALT levels in serum (Kushnerova *et al*., 2010; Chaabouni *et al.*, 2018; Vanavil *et al*., 2020 and Sayd-Ahmed *et al*., 2020). Also, Shannon *et al.* (2019) state that the hepatoprotective effect of SSP is primarily attributed to its pronounced antioxidant properties, which enhance the antioxidant defense mechanisms within hepatic cells. This is evidenced by a reduction in malonaldehyde (MDA) levels, and increasing hepatic catalase (CAT) activity and glutathione (GSH) levels. To confirm these results, many studies have shown the effect of different plant parts containing the same active secondary metabolites determined in SSA on reducing

the serum liver function enzymes activity induced by different toxic materials which could be attributed to their high level content of these active compounds (Sayed Ahmed *et al.*, 2016; Aly *et al*., 2017; Mahran *et al.*, 2018 and Elhassaneen *et al.*, 2010; 2020; 2021 a, c; 2023 a, b).

Effect of four weeks of intervention with *Sargassum subrependum* powder (SSP) on kidney functions of hepatotoxic rats

The impact of four weeks of intervention with *Sargassum subrependum* powder (SSP) on kidney functions of hepatotoxic rats is pointed out in Tables (5 and 6). The data indicate that rats injected with (B[*a*]P) displayed significantly elevated levels of creatinine (79.36%), urea (231.88%), and uric acid (170.05%) in comparison with the controls ($p \leq 0.05$). However, the administration of SSP at doses of 1.5, 3.0, and 6 g/100g of diet over four weeks period resulted in a significant reduction ($p \leq 0.05$) of the levels of these parameters by the rate of -36.28% (for creatinine); -51.91 % (for urea), and -48.42 % (foruric acid) in comparison to the normal control animals, correspondingly. The rate of reduction in all of these parameters exhibited a dose-dependent manner with the SSP concentrations.

These data are in agreement with a lot of authors who pointed out that B[*a*]P-induced kidney damage in the model animals (Bukowska & Duchnowicz, 2022 and Elhassaneen & Mahran, 2024). This damage could be caused by B[*a*]P induced oxidative stress (reactive oxygen species, ROS) which primarily initiates the release of various pro-inflammatory cytokines, which subsequently contribute to nephrotic inflammation and ultimately disrupts renal function. Also, Starko *et al.* (2019) found that oral administration of B[*a*]P in Swiss albino mice resulted in renal damage along with marked DNA fragmentation and integrity alteration in the kidney when comparison with the controls animals. Additionally, the elevation in serum urea concentration may be linked to the excessive breakdown of proteins and enzymes triggered by ROS. On the contrary, it was clear that treating rats with SSA resulted in a significant statistically reduction ($p \leq 0.05$) in the mean serum levels of urea, uric acid and creatinine when comparison to the positive controls. With this context, several studies reported that the positive treatment of SSA against kidney damage in hepatotoxic rats could be attributed to the bioactive compounds found. For example, alginates from brown algae administration resulted in, reduces levels of kidney functions (urea, uric acid and creatinine) (Prescott, 2000; Liu *et al*., 2012 and Harris *et al.*, 2019). It was observed that creatinine and uric acid levels were substantially reduced by fucoidan from brown algae (Abd Elmaksoud *et al*., 2020). Also, Akbar (2020) study the effect of fucoidan, a sulfated polysaccharide primarily derived from brown algae, highlighting its diverse pharmacological advantages in addressing various renal issues, including chronic renal failure and diabetic nephropathy. They found that concentrations of serum urea and creatinine were reduced in all groups. Furthermore, Prescott (2000) found that brown algae contain several chemicals that act as antioxidants. It is believed that these chemicals prevent damage to the body that can lead to diverse kidney problems, including chronic kidney failure and diabetic nephropathy. Chemicals in brown algae may also have effects on kidney inflammation, and they also found a significant decrease in creatinine and urea levels. Finally, Grune *et al*. (1997) reported that aryl hydrocarbon receptor (AhR) activation is involved in renal cell carcinoma and kidney diseases. Flavonoids measured in brown algae represent the most extensive components of AhR ligands, demonstrating their ability to inhibit AhR transformation (Farrugia, 2010). These might explain the SSP protective effect pathway against B[*a*]P-induced nephrotoxicity.

Table 5. Effect of four weeks of intervention with *Sargassum subrependum* powder (SSP) on kidney functions of hepatotoxic rats

Groups	Creatinine (mg/dl)	Urea (mg/dl)	Uric acid (mg/dl)
G1 (Normal control)	$0.63^{e} \pm 0.047$	$20.42^{e} \pm 2.804$	$3.64^{d} \pm 0.272$
G2 (Model control)	$1.13^{a} \pm 0.062$	$67.77^{a} \pm 2.131$	$9.83^{a} \pm 0.826$
G3 (SSP, 1.5% of BD)	$0.94^{b} \pm 0.028$	$55.78^{b} \pm 2.525$	$5.76^{b} \pm 0.597$
G4 (SSP, 3.0 % of BD)	$0.86^{c} \pm 0.022$	$43.62^{c} \pm 3.392$	$4.64^{c} \pm 0.272$
G5 (SSP, 6.0% of BD)	$0.72^{d} \pm 0.054$	$32.59^{d} \pm 2.113$	$5.07^{c} \pm 0.178$
LSD	0.049	3.277	0.506

The guides of the experimental groups are shown in Table (1). Each value represents mean ± SD (n=6). Means in the same column with different superscript letters differ significantly ($p<0.05$). LSD represents the least significant variation.

Table 6. Effect of four weeks of intervention with *Sargassum subrependum* powder (SSP) on kidney functions (as a percent of control) of hepatotoxic rats

Groups	Creatinine	Urea	Uric acid
G1 (Normal control)	------	------	-------
G2 (Model control)	79.36 ± 4.65	231.88 ± 19.96	170.05 ± 8.99
G3 (SSP, 1.5% of BD)	-16.81 ± 0.98	-17.69 ± 0.73	-41.40 ± 2.67
G4 (SSP, 3.0 % of BD)	-23.89 ± 0.08	-35.63 ± 2.67	-52.79 ± 8.34
G5 (SSP, 6.0% of BD)	-36.28 ± 2.65	-51.91 ± 3.90	-48.42 ± 4.55

The guides of the groups of experimental are shown in Table (1). The percentage of change (%) for the model control group is calculated in comparison with the controls, while it is calculated for the SPP-treated groups in comparison to the model controls.

Effect of four weeks of intervention with *Sargassum subrependum* powder (SSP) on bilirubin's level of hepatotoxic rats

Data in Tables (7 and 8) demonstrates the effect of four weeks of intervention with *Sargassum subrependum* powder (SSP) on bilirubin of hepatotoxic rats. Such data indicated that B[*a*]P-injected rats exhibited substantially ($p \leq 0.05$) raised levels of TB (142.50%), DB (41.66%) and IDB (185.71%) in comparison to the group of normal. Intervention with SSP (1.5, 3.0 and 6 g/100g diet) for four weeks significantly ($p \leq 0.05$) reduces the levels of these parameters by the rate of -36.08% (for TB); -29.41 % (for DB), and -37.50 % (for IDB) in comparison with the normal control animals, correspondingly. The reduction rate of all these parameters demonstrated a dose-dependent manner with the SSP concentrations.

Table 7. Effect of four weeks of intervention with *Sargassum subrependum* powder (SSP) on bilirubin level of hepatotoxic rats

Groups	TB (mg-dl)	DB (mg-dl)	IDB (mg-dl)
G1 (Normal control)	0.40^{c}±0.053	0.12^{b}±0.009	0.28^{c}±0.063
G2 (Model control)	0.97^{a}±0.057	0.17^{a}±0.027	0.8^{a}±0.056
G3 (SSP, 1.5% of BD)	0.67^{b}±0.054	0.16^{a}±0.006	0.51^{b}±0.051
G4 (SSP, 3.0 % of BD)	0.47^{c}±0.072	0.13^{b}±0.015	0.34^{c}±0.080
G5 (SSP, 6.0% of BD)	0.62^{b}±0.067	0.12^{b}±0.006	0.50^{b}±0.073
LSD	0.074	0.019	0.079

The guides of the experimental groups are shown in Table1. Each value represents mean ± SD (*n*=6). Means in the same column with different superscript letters differ significantly ($p<0.05$). LSD is the least significant difference.

Table 8. Effect of four weeks of intervention with *Sargassum subrependum* powder (SSP) on bilirubin level (as a percent of change) of hepatotoxic rats

Groups	TB	DB	IDB
G1 (Normal control)	-------	-------	------
G2 (Model control)	142.50 ± 10.45	41.66 ± 1.83	185.71 ± 21.67
G3 (SSP, 1.5% of BD)	-30.92 ± 4.88	-5.88 ± 0.66	-36.25 ± 4.87
G4 (SSP, 3.0 % of BD)	-51.54 ± 5.72	-23.53 ± 0.94	-57.50 ± 6.34
G5 (SSP, 6.0% of BD)	-36.08 ± 3.12	-29.41 ± 2.05	-37.50 ± 5.33

The guides of the experimental groups are shown in Table1. The percentage of change (%) for the model control group is calculated in comparison with the controls, while it is calculated for the SPP-treated groups in comparison to the model controls.

In general, bilirubin is a red-orange compound that forms during the normal catabolic pathway of heme breakdown in vertebrates. This pathway is essential for the body's elimination of waste products generated from the degradation of aged and/or abnormal red blood cells (RBCs) (Elhassaneen *et al.,* 2024). Bilirubin is produced through the action of biliverdin reductase on biliverdin, another byproduct of heme catabolism, which can be oxidized to revert to biliverdin. It is a potent antioxidant activity and the main physiologic role is as a cellular antioxidant (Stocker *et al*., 1987; Baranano *et al*., 2002 and Sedlak *et al*., 2009). In this context, several animal studies proposed that eliminating bilirubin results in endogenous oxidative stress (Chen *et al*., 2018). Thus, antioxidant activity exhibited by bilirubin could be especially important in the brain, because it prevents toxicity and neuronal death by scavenging superoxide during N-methyl-D-aspartic acid neurotransmission *(*Vasavda *et al*., 2019). The normal value of bilirubin in the blood is 21 µmol/L, higher bilirubin in the blood than normal leads to the appearance of jaundice symptoms due to the accumulation of bilirubin in the skin and conjunctiva of the eye. Hyperbilirubinemia refers to an elevated concentration of bilirubin in the blood, which may indicate increased levels of conjugated, unconjugated, or both forms of bilirubin. The causes of hyperbilirubinemia include prehepatic, intrahepatic, and post-hepatic (Doumas *et al*., 1971). Prehepatic leadings are primarily linked to an elevation in unconjugated (indirect) bilirubin as the result of hemolysis or increased breakdown of red blood cells. Intrahepatic leadings can be associated with elevated levels of either conjugated bilirubin, unconjugated bilirubin, or both. Conversely, post hepatic causes are typically associated with increased levels of conjugated bilirubin resulting from significant bile duct obstruction, biliary stricture severe liver failure with cirrhosis and pancreatitis. Data from the current study declared that treating rats with SSA led to a statistically significant ($p \leq 0.05$) decrease in the mean values of bilirubin compared to those in the B[*a*]P model group. With this context, several studies reported that the positive treatment of SSA against bilirubin's rising level in hepatotoxic rats could be attributed to their bioactive compounds. For example, Carreres *et al*. (2021) showed that the nutritional composition containing brown algae reduces the accumulation of liver fat by modulating fat metabolism and reducing total bilirubin as well as direct and indirect in mice with hepatotoxicity. Also, Carreres *et al*. (2021) showed that brown algae reduce hepatic lipids, and reduce total and direct bilirubin through experiments with biological mice.

Effect of four weeks of intervention with *Sargassum subrependum* powder (SSP) on immunological proteins of hepatotoxic rats

Data in Tables (9 and 10) demonstrates the effect of four weeks of intervention with *Sargassum subrependum* powder (SSP) on the immunological proteins of hepatotoxic rats. Such data indicated that B[*a*]P-injected rats exhibiting significantly ($p \leq 0.05$) decreased levels of TP (-31.01%), Alb (-31.15%) and Glb (-30.62%) in comparison to the group of normal. Intervention with SSP (1.5, 3.0 and 6 g/100g diet) for four weeks significantly ($p \leq 0.05$) increased the levels of these parameters by the rate of 33.66% (for TP); 33.94 % (for Alb), and 33.33 % (for Glb) in comparison with the normal controls animals, correspondingly. The rate raises in all of these parameters exhibited a dose-dependent manner with the SSP Concentrations.

Table 9. Effect of different concentrations of brown algae powder on immunological proteins of hepatotoxic rats

Groups	TP (g-dl)	Alb (g-dl)	Glb (g-dl)	Alb/Glb ratio
G1 (Normal control)	7.19^{a}±0.193	3.98^{a}±0.086	3.20^{a}±0.212	1.25^{a}±0.101
G2 (Model control)	4.96^{e}±0.091	2.74^{e}±0.142	2.22^{b}±0.208	1.26^{a}±0.166
G3 (SSP, 1.5% of BD)	5.34^{d}±0.142	2.89^{d}±0.127	2.44^{b}±0.220	1.20^{a}±0.142
G4 (SSP, 3.0 % of BD)	6.39^{c}±0.341	3.36^{c}±0.094	3.03^{a}±0.374	1.14^{a}±0.161
G5 (SSP, 6.0% of BD)	6.63^{b}±0.216	3.67^{b}±0.053	2.96^{a}±0.183	1.24^{a}±0.069
LSD	0.236	0.131	0.294	0.161

The guides of the experimental groups are shown in Table (1). Each value represents mean ± SD (n=6). Means in the same column with different superscript letters differ significantly ($p<0.05$). LSD is the least significant difference.

Table 10. Effect of different concentrations of brown algae powder on immunological proteins (as a percent of change) of hepatotoxic rats

Groups	TP	Alb	Glb	Alb/Glb ratio
G1 (Normal control)	------	-----	------	------
G2 (Model control)	-31.01 ± 3.67	-31.15 ± 3.23	-30.62 ± 2.20	0.80 ± 0.09
G3 (SSP, 1.5% of BD)	7.66 ± 0.64	5.47 ± 0.45	9.90 ± 0.45	-4.76 ± 0.21
G4 (SSP, 3.0 % of BD)	28.83 ± 2.17	22.62 ± 2.18	36.49 ± 3.11	-9.52 ± 0.39
G5 (SSP, 6.0% of BD)	33.66 ± 3.09	33.94 ± 4.20	33.33 ± 2.11	-1.58 ± 0.08

The guides of the groups of experimental are shown in Table1. The percentage of change (%) for the model control group is calculated in comparison with the controls, while it is calculated for the SPP-treated groups in comparison to the model controls.

In similar studies, several authors found that B[*a*]P induced significant reductions in the serum albumin composition in comparison to the normal animals (Hussien *et al.,* 2021 and Elhassaneen *et al.,* 2016b; 2024). Also, other studies have shown that CCl_4-induced liver injury leads to a significant reduction in serum albumin levels (Wang *et al*., 2007; Abd El-Fatah, 2013 and Elhassaneen *et al*., 2021c). Hypoalbuminemia is often observed in advanced chronic liver diseases, suggesting that reductions in total protein (TP) and albumin (Alb) can serve as valuable indicators of the severity of cellular dysfunction in these conditions. Albumin has a crucial role as a metal-binding protein; it acts as an antioxidant by tightly binding copper and weakly binding iron, thereby mitigating free radical reactions associated with these metals and inhibiting copper-dependent lipid peroxidation (Gutteridge and Wilkins, 1983). Globulins, a family of higher molecular weight proteins produced by both the liver and the immune system, along with albumins and fibrinogen, constitute the major blood proteins (Kakkar *et al*., 1998). In the current study, the administration of SSP resulted in a significant rise ($p \leq 0.05$) in serum albumin levels, indicating its potential to prevent or repair hepatocyte damage. With this context, Jiménez-Escring *et al*. (2011) found that brown algae contain bioactive components that comprise polyphenols, peptides, and polysaccharides, and many of these active compounds have beneficial roles with many health benefits and increase immune proteins such as Alb and Glb. Also, Wijesinghe and Jeon (2012) observed that functional polysaccharides, such as fucoidan and alginic acid, derived from seaweed, exhibit various biologically beneficial properties, besides anticoagulant, anti-inflammatory, antiviral, and antitumor properties, and improve immune functions (immune proteins) to mice with hepatotoxicity. Furthermore, Devillé *et al*. (2004) found that brown algae is rich in protein, minerals, and contains several bioactive compounds. These compounds include alginate and polymers containing fucose, sulphate, and laminarin, and affect the increase in immune proteins i.e. TP, Alb and Glb. Finally, Elhassaneen *et al.* (2024) found that brown algae contain alginate in their cell wall and also contain fucoxanthin that works to reduce Alb/Glb ratio in hepatotoxic rats. Such a role of SSA in manipulating the plasma proteins, especially Alb, is critically important, as human serum albumin constitutes approximately 50% of blood plasma proteins. Albumin functions as a transport protein, binding various ligands and facilitating their transport, including fatty acids, hormones, water, bilirubin, pharmaceuticals, thyroxine (T4), and cations (Ca^{2+}, K^{+}, and Na^{+}). Consequently, the primary function of albumin is to regulate the oncotic pressure of blood (Farrugia, 2010).

Effect of four weeks of intervention with *Sargassum subrependum* powder (SSP) on glutathione (GSH) and malondialdehyde (MDA) of hepatotoxic rats

The impact of four weeks of intervention with *Sargassum subrependum* powder (SSP) on GSH and MDA of hepatotoxic rats was outlined in Tables (11 and 12). It can be noticed about this data that B[*a*]P-injected rats demonstrated significantly ($p \leq 0.05$) decreased levels of GSH (-86.98%) and increased levels of MDA (2984.37%) in comparison to the normal group. Intervention with SSP (1.5, 3.0 and 6 g/100g diet) for four weeks significantly ($p \leq 0.05$) increased the levels of GSH activities by the rate of 485.93% and decreased the levels of MDA by -90.67 % in comparison with the normal controls animals, correspondingly.

Table 11. Effect of four weeks of intervention with *Sargassum subrependum* powder (SSP) on glutathione (GSH) and malondialdehyde (MDA) of hepatotoxic rats

Groups	GSH (ng/ml)	MDA (nmol/ml)
G1 (Normal control)	205.32^{a}±11.390	0.32^{d}±0.059
G2 (Model control)	26.73^{e}±5.468	9.87^{a}±0.848
G3 (SSP, 1.5% of BD)	69.08^{d}±11.436	5.41^{b}±0.411
G4 (SSP, 3.0 % of BD)	124^{c}±5.001	2.15^{c}±0.450
G5 (SSP, 6.0% of BD)	156.62^{b}±12.112	0.92^{d}±0.077
LSD	11.166	0.624

The guides of the experimental groups are shown in Table (1). Each value represents mean ± SD (n=6). Means in the same column with different superscript letters differ significantly ($p<0.05$). LSD is the least significant difference; GSH, glutathione, MDA, malondialdehyde.

Table 12. Effect of four weeks of intervention with *Sargassum subrependum* powder (SSP) on glutathione (GSH) and malondialdehyde (MDA) (as a percent of change) of hepatotoxic rats

Groups	GSH	MDA
G1 (Normal control)	------	------
G2 (Model control)	-86.98 ± 6.78	2984.37 ± 23.78
G3 (SSP, 1.5% of BD)	158.43 ± 9.14	-45.18 ± 3.11
G4 (SSP, 3.0 % of BD)	363.89 ± 28.45	-78.22 ± 5.77
G5 (SSP, 6.0% of BD)	485.93 ± 19.65	-90.67 ± 2.11

The guides of the groups of experimental are shown in Table1. The percentage of change (%) for the model control group is calculated in comparison with the controls, while it is calculated for the SPP-treated groups in comparison to the model controls.

The rate of rise of GSH and decrease of MDA demonstrated a dose-dependent manner with the SSP concentrations. In general, GSH has received more attention concerning its biosynthesis and diverse intracellular functions (Mannervik, 1985 and Elhasaneen, 1996). Its role in the detoxification process is central, as it involves the conjugation of toxicants with electrophilic intermediates, including B[*a*]P and excreted to the body outside. Also, GSH has important antioxidant functions through its role that extends to the functioning of the antioxidant enzyme system, including glutathione peroxidase and glutathione reductase. Furthermore, GSH acts as a non-enzymatic scavenger of reactive oxygen species (ROS) (Elhasaneen, 1996). Results of the current study indicated that injecting the rats with B[*a*]P generated ROS, as demonstrated by reduced GSH levels. Such data are in agreement with what was pointed out by Elhassaneen *et al*. (2018), that exposing rats to B[*a*]P leads to a significant loss in GSH by the rate of -38.35% in comparison to normal rats. On the contrary, a human survey study on B[*a*]P-associated oxidative stress has utilized assays to measure either biomarkers or the end-products of free radical-mediated oxidative processes (Elhassneen, 2004). In this context, lipid peroxidation markers, such as MDA, are among the most significant compounds and serve as major products resulting from the oxidation of polyunsaturated fatty acids. Several studies reported that MDA elevated in plasma rats injected with B[*a*]P (Elhassaneen *et al*., 2023a, b and Mahran & Elhassaneen, 2023). Several decades ago, MDA is reported to be a mutagenic and carcinogenic compound (Shamberger *et al*., 1974). Data of the currently studied exhibited that treatment with SSP elevated the GSH and decreased the MDA levels in B[*a*]P treated rats. These results are in agreement with Fitton (2003) who showed the results that the extract of *Sargassum* species demonstrated a significant impact in reducing MDA levels in white rats. It was found that when MDA levels decreased, liver function was improved in rats with hepatotoxicity. Also, Yuan *et al*. (2018) found that brown algae contains several bioactive compounds that act as antioxidants. It is believed that these compounds prevent damage to the body that can lead to cancer and therefore increase the level of glutathione in mice with hepatotoxicity. Furthermore, it was discovered that the brown alga *Sargassum* sp. exhibits the highest antioxidant activity in comparison to red and green algae, with polyphenol compounds identified as the primary antioxidant components in *Sargassum* sp. that has higher glutathione and lower malondialdehyde to rats with hepatotoxicity. Data from all previous studies prove that SSP is a promising and successful instrument that could be used in the prevention of cells/hepatocytes from oxidative stress due to exposure to B[*a*]P.

Effect of four weeks of intervention with *Sargassum subrependum* powder (SSP) on red blood cells (RBCs) antioxidant enzymes of hepatotoxic rats

Data in Tables (13 and 14) demonstrate the effect of four weeks of intervention with *Sargassum subrependum* powder (SSP) on RBCs antioxidant enzymes of hepatotoxic rats. Such data indicated that B[*a*]P-injected rats demonstrated significantly ($p\leq0.05$)

decreased levels of SOD (-78.14%), CAT (-97.35%) and GPX (-89.82%) in comparison.

To the normal group. Intervention with SSP (1.5, 3.0 and 6 g/100g diet) for four weeks significantly ($p \leq 0.05$) increased the levels of these parameters by the rate of 309.93% (for SOD); 2411.42 % (for CAT), and 634.77% (for GPX) in comparison to the control of normal animals, correspondingly. The rate of increase in all these parameters was observed to exhibit a dose-dependent manner with the SSP concentrations. These data follow a lot of previous authors who observed that B[*a*]P-induced reduction in RBCs antioxidant enzymes activity in the model groups (Elhassaneen, 2004; Chandini *et al*., 2008; Elhassaneen *et al*., 2016b; 2018; Shahid *et al*., 2016; Bai *et al*., 2021; Bukowska & Duchnowicz, 2022 and Elhassaneen & Mahran, 2024). RBCs can be viewed as carriers of circulating antioxidants to defend against the many dangers it is exposed to, which include: elevated ROS, damaged constituents, and changed membrane lipids structure which makes them susceptible to peroxidation (Elhassaneen and Mahran, 2024). The noticeable suppression of RBCs antioxidant enzymes activity under B[*a*]P subjection could be attributed to excessive ROS production during B[*a*]P metabolism, as confirmed by increased levels of blood oxidants (MDA) and alteration of the redox state which led to oxidative stress. All of these factors ultimately induced depletion of the antioxidant enzymes in RBCs (Elhassaneen, 2004; Kiruthiga *et al*., 2015; Fayez, 2016 and Elhassaneen *et al*., 2023a, b). On contrary, it was clear that treating rats with SSA led to a statistically substantial ($p \leq 0.05$) raise in the mean values of RBC antioxidant enzyme activity compared to those in a B[*a*]P model group. With this context, several studies reported that the positive treatment of SSA against RBCs antioxidant defense system damage in hepatotoxic rats could be attributed to their bioactive compounds found. For example, Yildiztekin *et al*. (2018) found that phlorotannins are the main phenolic compounds of brown algae and have an antioxidant role. It has been observed that the aqueous extract of *Sargassum* sp. substantially reduces lipid peroxidation, and phlorotannin increases levels of GPX, CAT, and SOD, thus improving liver functions in hepatotoxic albino rats. Also, Kan *et al*. (2019) found that fucoxanthin present in brown algae such as *Sargassum* genus enhance the enzymatic antioxidant activity of SOD in rats. Furthermore, McCord *et al*. (1971) found that in the cell wall of brown algae, cell cytoplasm, and mitochondria there are the most effective antioxidants, which are the enzyme SOD, CAT and GPX. These components work to improve liver toxicity diseases and therefore they found a high percentage of SOD, CAT, and GPX in infected mice. Finally, Swaminathan *et al*. (2021) showed that brown algae have numerous biological activities, such as anti-osteoporosis, anti-microbial, anti-inflammatory, anti-tumor, and contain antioxidants which work to increase the ratio of SOD and CAT as well as improve the liver functions in biological mice with hepatotoxicity.

Table 13. Effect of four weeks of intervention with *Sargassum subrependum* powder (SSP) on red blood cells (RBCs) antioxidant enzymes of hepatotoxic rats

Groups	SOD (U/ml)	CAT (ng/ml)	GPX (U/ml)
G1 (Normal control)	214.65^{a}±13.119	13.23^{a}±1.182	243.27^{a}±12.106
G2 (Model control)	46.91^{e}±5.355	0.35^{d}±0.058	24.76^{e}±4.916
G3 (SSP, 1.5% of BD)	83.68^{d}±5.475	0.89^{d}±0.117	78.10^{d}±7.538
G4 (SSP, 3.0 % of BD)	146.1^{c}±4.360	4.86^{c}±1.404	134.16^{c}±9.282
G5 (SSP, 6.0% of BD)	192.3^{b}±11.310	8.79^{b}±0.936	181.93^{b}±11.354
LSD	11.178	1.112	11.564

The guides of the experimental groups are shown in Table (1). Each value represents mean ± SD (*n*=6). Means in the same column with different superscript letters differ significantly ($p<0.05$). LSD is the least significant difference.

Table 14. Effect of four weeks of intervention with *Sargassum subrependum* powder (SSP) on red blood cells (RBCs) antioxidant enzymes (as a percent of change) of hepatotoxic rats

Groups	SOD	CAT	GPX
G1 (Normal control)	-------	------	-------
G2 (Model control)	-78.14 ± 2.56	-97.35 ± 5.23	-89.82 ± 3.67
G3 (SSP, 1.5% of BD)	78.38 ± 4.11	154.28 ± 10.34	215.43 ± 5.87
G4 (SSP, 3.0 % of BD)	211.44 ± 23.76	1288.57 ± 33.45	441.84 ± 7.23
G5 (SSP, 6.0% of BD)	309.93 ± 19.10	2411.42 ± 29.67	634.77 ± 21.74

The guides of the groups of experimental are shown in Table1. The percentage of change (%) for the model control group is calculated in comparison with the controls, while it is calculated for the SPP-treated groups in comparison to the model controls.

Histopathological examination

Effect of *Sargassum subrependum* powder (SSP) on B[*a*]P-induced histological alterations in liver tissues

Figure (1) illustrates the effect of *Sargassum subrependum* powder (SSP) on B[*a*]P-induced histological alterations in liver tissues. Light microscopic examination of liver sections from group 1 rats revealed the normal histological architecture of the hepatic lobule (Photo 1). In contrast, the livers of group 2 rats exhibited hepatocellular vacuolar degeneration (Photo 2), hyperplasia of the biliary epithelium, and portal infiltration by inflammatory cells (Photo 3). Additionally, the livers of group 3 rats displayed sporadic vacuolar degeneration of hepatocytes along with small focal hepatocellular necrosis accompanied by inflammatory cell infiltration (Photo 4). In Otherwise, sections from group4 exhibited mild histopathological alterations characterized by vacuolar degeneration of sporadic hepatocytes (Photo 5). Likewise, liver sections from group 5 showed vacuolar degeneration of sporadic hepatocytes (Photo 6). Data of the present study largely matches that found by Elhassaneen and Mahran (2024). They observed that liver tissue of rats that were exposed to B[*a*]P exhibited severe histopathological changes that involved vacuolar degeneration of hepatocytes, focal hepatocellular necrosis associated with inflammatory cells infiltration, activation of Kupffer cells, fibroplasia in the portal triad, and appearance of newly formed bile ductules. Also, Kiruthiga *et al*. (2015) pointed out that liver sections of rats that were exposed to B[*a*]P observed hepatic necrosis, hepatocyte degeneration, loss of hepatic plate architecture, and infiltration of mononuclear cells. Furthermore, Riordan and Williams (2002) reported that hepatocytes in B[*a*]P-injected rats showed apoptosis which is characterized by pyknotic nuclei, ballooning degeneration and swollen wispy cytosol. All of such histopathological changes, and the progression of liver damage, could be attributed to oxidative stress. In this context, Liu Y *et al*. (2011) and Shargel *et al*. (2016) found the liver comes into contact with injury due to oxidative stress mainly in its parenchymal cells besides Kupffer cells, endothelial cells, and stellate cells. Also, lipid peroxidation as the result of oxidative stress stimulates cell proliferation and collagen synthesis. Collagen accumulation in the hepatocytes leads to the development of liver fibrosis and ultimately results in liver cirrhosis (Hajam *et al*., 2022). On the contrary, B[*a*]P-hepatoxic rats treated with SSP recorded various degrees of improvement in histopathological changes and mitigated the degenerative alterations in liver tissues depending on SSP dose. It exhibited only slight vacuolar degeneration of sporadic hepatocytes within specific liver sections, while others displayed a normal histological architecture of the hepatic lobule. These improvements in liver tissue histoarchitecture may be attributed to the antioxidant activities recorded by SSP (El-Gamal, 2020; Abd Elalal *et al*., 2021; Abdelrahman, 2022; Gad Alla, 2023; Hussien *et al.*, 2021 and Elhassaneen *et al*., 2021b; 2023a, b; 2024). All of these studies demonstrated that bioactive compounds in brown algae has the ability to reduce oxidative stress and subsequent cytotoxicity, thereby protecting intact hepatocytes or cells that have not yet experienced irreversible damage. They also reported that brown algae, powder and extracts, act as a scavenger of free radicals and subsequently regulate the activity of enzymes linked to the progression of cellular injury, fibrosis, and cirrhosis. Additionally, these studies proposed that the potential hepatoprotective mechanisms of brown algae may involve inhibition of lipid oxidation, elevation of intracellular glutathione fractions content, regulation of cellular membrane permeability, enhancement of the cellular membrane stability in the face of xenobiotic damage, and hindrance of stellate hepatocyte transformation into my fibroblasts. This transformation is responsible for collagen fiber deposition, which may lead to cirrhosis (Mahran and Elhassaneen, 2023). Our observation may concomitant with several previous studies which proposed that brown algae exhibit promising antifibrotic activity and anti- apoptosis in experimental liver injury due to its active secondary metabolites composition (Elhassaneen *et al*., 2023 a,b and Gad Alla, 2023). Data from the present study demonstrated that SSP effectively normalized liver functions and partially repaired hepatic tissue damage as well as its protective effect might be more pronounced with higher doses.

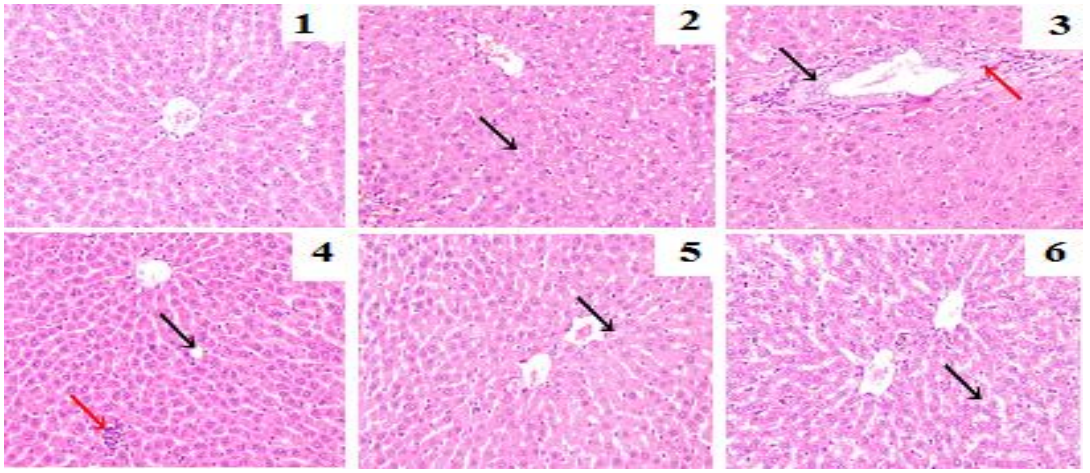

Fig. 1. Effect of *Sargassum subrependum* powder (SSP) on B[*a*]P-induced histological alterations in liver tissues (H & E X 400)

Photomicrograph of **Photo 1.** liver of rat from group 1 pointed out the normal histological architecture of hepatic lobule, **Photo 2.** liver of rat from group 2 pointed out hepatocellular vacuolar degeneration (arrow), **Photo 3**. liver of rat from group 2 pointed out hyperplasia of biliary epithelium (black arrow) and portal infiltration with inflammatory cells (red arrow), **Photo 4.** liver of rat from group 3 pointed out vacuolar degeneration of sporadic hepatocytes (black arrow) and small focal hepatocellular necrosis associated with inflammatory cells infiltration (red arrow), **Photo5.** liver of rat from group 4 pointed out vacuolar degeneration of sporadic hepatocytes (black arrow), **Photo 6.** liver of rat from group 5 pointed out vacuolar degeneration of sporadic hepatocytes (black arrow).

Effect of *Sargassum subrependum* powder (SSP) on B[*a*] P-induced histological alterations in kidney tissues

Figure (2) illustrates the effect of *Sargassum subrependum* powder (SSP) on B[*a*]P-induced histological alterations in kidney tissues. Microscopic examination of the kidneys from group 1 rats revealed a normal histological structure of the renal parenchyma (Photo 1). In contrast, the kidneys of group 2 rats exhibited significant vacuolar degeneration of the epithelial lining of the renal tubules as well as congestion of renal blood vessels (Photos 2 and 3). Additionally, the kidneys of rats from group 3 described congestion of renal blood vessels (Photo 4). Otherwise, examined renal tissues of rats from group 4 revealed vacuolar degeneration of the epithelial lining of some renal tubules (Photo 5). On the other hand, sections of renal tissue of rats from group 5 exhibited no histopathological alterations (Photo 6). Data of the present study largely matches that found by Elhassaneen and Mahran (2024) who observed that kidney tissue of rats that were exposed to B[*a*]P exhibited severe histopathological changes marked vacuolization of epithelial lining renal tubules, congestion of the glomerular tufts and intertubular inflammatory cell infiltration. Also, Elhassaneen *et al*. (2021c) noticed that B[*a*]P injected-rats resulted in the appearance of various detrimental consequences in the kidney tissue including disorganized glomeruli, congested blood capillaries, and tubules had lost their brush border and exhibited an obstructed lumen. Additionally, Andrade *et al*. (2007) reported that the kidney of rats injected B[*a*]P observed multiple protein casts within the tubular lumen indicating nephritic glomerular dysfunction. With this context, Hajam *et al*. (2022) and Elhassaneen & Mahran (2024) reported that kidneys come into contact with injury due to oxidative stress which is implicated in the pathophysiology of various disorders including glomerular- and tubule-interstitial nephritis, renal ischemia, uremia, proteinuria, tubular necrosis, apoptosis, and renal failure. They also indicated that kidneys are adversely affected by oxidative stress primarily due to the activation of inflammatory cells and pro-inflammatory cytokine production owing to ROS generation, resulting in an initial inflammatory stage. With this context, Kwon *et al*. (2013) and Hajam *et al*. (2022) when kidney tissues are exposed to chronic oxidative stress stimuli the outcome is an initial inflammatory stage followed by excessive production of fibrotic tissue. Also, El Maaiden *et al*. (2019) stated that oxidative stress exacerbates advanced glomerular damage, tubular atrophy, and interstitial. On the contrary, kidneys of rats from the B[*a*]P + SSP showed various degrees of improvement in histopathological changes depending on SSP dose. Rats with SSP at 6.0% showed no histopathological changes. The bioactive compounds of brown algae include phenolics, carotenoids, anthocyanins and alkaloids (El-Gamal, 2020; Abdelrahman, 2022; Elhassaneen *et al*., 2021 a; 2023 a, b and Gad Alla, 2023).

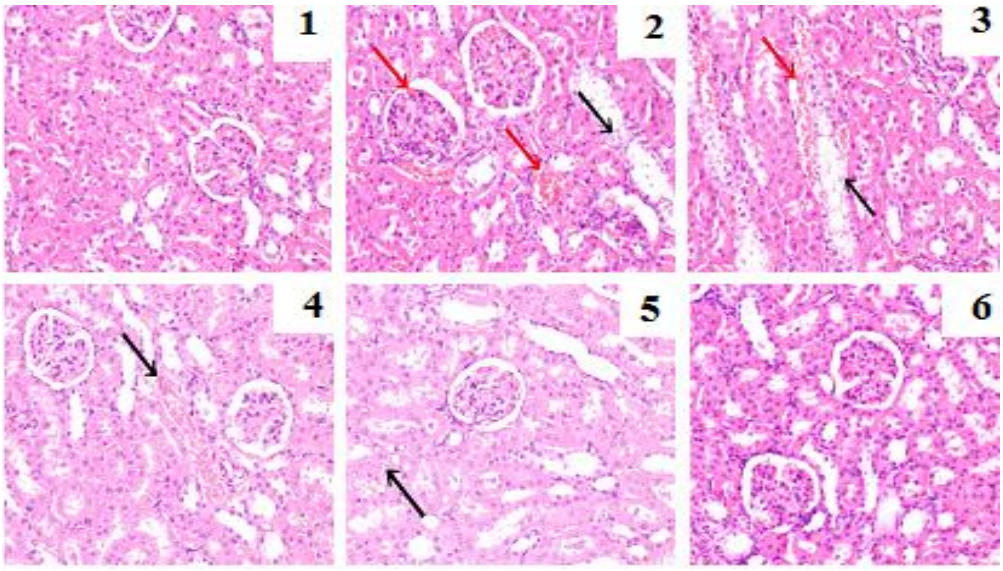

Figure 2. Effect of *Sargassum subrependum* powder (SSP) on B[*a*]P-induced histological alterations in kidney tissues (H & E X 400)

Photomicrograph of **Photo 1.** kidney of rat from group 1 pointed out the normal histological structure of renal parenchyma, **Photo 2.** kidney of rat from group 2 pointed out vacuolar degeneration of epithelial lining renal tubules (black arrow) as well as congestion of glomerular tufts and renal blood vessels (red arrow), **Photo 3.** kidney of rat from group 2 pointed out vacuolar degeneration of epithelial lining renal tubules (black arrow) as well as congestion of renal blood vessels (red arrow). **Photo 4.** kidney of rat from group 3 pointed out congestion of renal blood vessels (arrow). **Photo 5.** kidney of rat from group 4 pointed out vacuolar degeneration of epithelial lining some renal tubules (black arrow). **Photo 6.** kidney of rat from group 5 pointed out no histopathological alterations.

Several studies exhibited ameliorative effects of such compounds on tubular necrosis in experiencing various toxins -induced acute nephrotoxicity (Østerby & Gundersen, 1978; Elhassaneen *et al.,* 2010; 2021b). Data from the present study proposed that histopathological renoprotective effect of SSP could be ascribed to its potent antioxidants that effectually counteract the generation of free radicals or reactive metabolites released during B[*a*]P biotransformation.

CONCLUSION

Benzo[*a*]pyrene (B[*a*]P) is a primary representative of polycyclic aromatic hydrocarbons (PAHs) formed during food preparation and processing methods such as baking, frying, grilling, or smoking. Additionally, exposure to B[*a*]P is linked to the rise of liver toxicity and carcinogenic effects in all vertebrates. Plant-derived active secondary metabolites have recently garnered substantial interest due to their capacity to counteract the adverse effects of the pollutants. Data from the current study demonstrated that exposure to B[*a*]P induced significant injuries to the liver and kidney of albino rats. Such injuries are leading to disruptions in various biochemical markers and substantial alterations in the histological structure of the organ tissue. On the contrary, feeding intervention with SSP at concentrations 1.5%, 3.0 and 6.0 g/100 diet exhibited remarkable hepatoprotective and nephroprotective effects against B[*a*]P-induced hepatotoxicity. The rate of improvement in all biochemical and histopathological parameters demonstrated a dose-dependent relationship with the SSP intervention. These findings may provide new insights into the development of a new liver and kidney prevention strategy using SSP as a dietary supplement for individuals at risk of B[a]P exposure.

Authors' contribution

Yousif Elhassaneen contributed to the development of the study protocol, oversaw the experimental work in laboratory, retrieved conceptual information, reviewed and validated the results and analyses statistical, and prepared a draft of the manuscript while conducting a critical review. Asmaa Menusy performed the laboratory experiments, collected, tabulated, analyzed, and interpreted the results, and assisted in retrieving conceptual information as well as drafting the manuscript. Amal Nasef Zaki was involved in proposing the study protocol, retrieving conceptual information, contributing to the study's concept and design, validating the results, and preparing the draft manuscript.

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Abbreviations

B[*a*]P: benzo[a]pyrene
ALT: Alanine aminotransferase
ALP: Alkaline phosphatase
BWG: Body weight gain
DNA: Deoxyribonucleic acid
FER: Feed efficiency ratio
GSH: Reduced glutathione
GPX: Glutathione peroxidase
ROS: Reactive oxygen species
TBARS: Thiobarbituric acid reactive substances
SSP: *Sargassum subrepandum* powder Alb: Albumin
AST: Aspartate aminotransferase
BD: Basal diet
FI: Feed intake
GGT: Gamma-glutamyl transferase
RNA: Ribonucleic acid
MDA: Malondialdehyde
SOD: Superoxide dismutase
TB: total bilirubin

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الملخص العربي

الآثار الوقائية المحتملة لمسحوق الطحالب البنية (سرجاسم سبريباندیم) على الخلل الوظيفي الكبدي والكلوى الناجم عن البنزو [أ] البيرين في الفئران

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يُعد البنزوبيرين (B[*a*]P) ممثلًا أساسيًا للهيدروكربونات العطرية متعددة الحلقات (PAHs) التي يتم إنتاجها أثناء طرق تحضير وتجهيز الطعام المختلفة، مثل الخبيز والقلي والشواء والتدخين. وقد ارتبط التعرض لـ B[*a*]P بتسمم الكبد والتأثيرات المسرطنة في جميع أنواع الفقاريات. تهدف هذه الدراسة إلى استكشاف التأثيرات الوقائية المحتملة لمسحوق الطحالب البنية (*Sargassum subrepandum*) على اختلال وظائف الكبد والكلى الناجم عن البنزوبيرين في الفئران. تم تقسيم ثلاثين فأرًا أبيض ذكرًا إلى مجموعتين رئيسيتين، المجموعة الأولى (G1، ٦ فئران، كمجموعة ضابطة سالبة) تم إطعامها النظام الغذائي الأساسي (BD) والمجموعة الرئيسية الثانية (٢٤ فأرًا)، التي تم إعطاؤهاB[*a*]P ، تم توزيعها على أربع مجموعات متساوية (٦ فئران لكل منها) على النحو التالي: المجموعة ٢ (G2) عملت كمجموعة تحكم موجبة (نموذج الفئران المصابة بسمية الكبد)، بينما تلقت المجموعات (٣–٥) مسحوق *Sargassum subrepandum* (SSP) بتركيزات ١,٥ و ٣,٠ و ٦ جم / ١٠٠ جم من النظام الغذائي لمدة ٢٨ يومًا لكل منها على التوالي. أدى التعرض لـ B[*a*]P بشكل ملحوظ ($p \leq 0.05$) إلى زيادة أنشطة إنزيمات الكبد (AST (%72.27، ALT (%95.94)، ALP (%243.01)،GGT (%670.08)، مؤشرات وظائف الكلى [اليوريا في سيرم الدم (٢٣١,٨٨٪)، حمض البوليك (١٧٠,٠٥٪) والكرياتينين (٧٩,٣٦٪)]، وتركيز المالونالدهيد (2984.37%) (مصحوبة بتغيرات نسيجية مرضية شديدة في أنسجة الكبد والكلى مقارنة بمجموعة التحكم الطبيعية. كما تم تسجيل انخفاض معنوى ($p \leq 0.05$) في الإنزيمات المضادة للأكسدة (-78.14%) SOD، CAT(-97.35%)، GPX (-89.82%)، GSH (-86.98%)، والبروتينات المناعية [الألبومين (−٣١,١٥٪) والغلوبيولين (−٣٠,٦٢٪]. أظهر العلاج بـ SSP لمدة ٢٤ يومًا تحسنًا كبيرًا ($p \leq 0.05$) في جميع هذه المؤشرات والبنية النسيجية للكبد والكلى لدى الفئران .أظهر التحسن في جميع المؤشرات المقيمة استجابة تعتمد على الجرعة المستخدمه SSP. وفي النهاية، تشير النتائج الحالية من هذه الدراسة إلى أن العلاج بـ SSP بالتركيزات المقيمة خفف بشكل فعال من الإصابات الكيميائية الحيوية والنسيجية للكبد والكلى الناجمة عنB[*a*]P، مما يسلط الضوء على إمكانات هذا التدخل.

الكلمات المفتاحية: إنزيمات الكبد، وظائف الكلى، البيليروبين، إنزيمات مضادة للأكسدة، بروتينات البلازما، علم الأمراض النسيجي.