

Full Length Research Paper

Hepatoprotective and hypolipidemic effects of *Spirulina platensis* in rats administered mercuric chloride

Bashandy S. A.^{1,3*}, Alhazza I. M.¹, El-Desoky G. E.² and Al-Othman Z. A.²

¹Zoology Department, College of Science, King Saud University, P. O. Box 2455, Riyadh 11451, Saudi Arabia.

²Chemistry Department, College of Science, King Saud University, P. O. Box 2455, Riyadh 11451, Saudi Arabia.

³Pharmacology Department, National Research Center, Cairo, Egypt.

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In the present study *Spirulina platensis* has been investigated as a possible modifier of mercury induced hepatic damages and alteration of lipid profile in albino rats. The results revealed that the rats treated with mercuric chloride (HgCl₂) showed a significant increase in levels of blood hydroperoxide, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total cholesterol (TC), triglycerides and low density lipoprotein-cholesterol (LDL-C). Moreover, hepatic malondialdehyde (MDA) concentration of HgCl₂ group elevated significantly. On the other hand, plasma protein, high density lipoprotein-cholesterol (HDL-C) and hepatic glutathione (GSH) of HgCl₂ treated group showed a significant decrease compared to the control group. Mercury intoxication induces some pathological alterations in the liver as necrosis and cytoplasmic vacuolization. The rise in plasma hepatic enzymes, cholesterol, triglycerides, LDL-C, hydroperoxide, and histopathological changes were significantly attenuated by *Spirulina*. Moreover, the levels of plasma HDL-C and protein and hepatic glutathione in *Spirulina*+HgCl₂ group showed a significant increase as compared with HgCl₂ group. *Spirulina* significantly alleviated the hepatotoxicity induced by HgCl₂ and modified the lipid profile through its antioxidant properties.

Key words: *Spirulina platensis*, mercuric chloride, hydroperoxide, liver enzymes, glutathione, cholesterol, triglycerides, HDL, LDL.

INTRODUCTION

Mercury (Hg) is a highly toxic metal (Al-Othman et al., 2011; Nabi et al., 2010, 2011), results in a variety of adverse health effects including neurological, renal, respiratory, immune, dermatologic, reproductive and development sequel (Risher and Amler, 2005). Inorganic mercury presents in the environment is a well established toxicant to human health (WHO, 1991). Hg can cause biochemical damage to tissues through diverse mechanisms such as lipid peroxidation (Huang et al., 1996), formation of reactive oxygen species (Woods et al., 1990), altering protein synthesis (Yee and Choi, 1996) and via binding to thiol groups (Zalups, 2000). Hg

accumulated in the liver and elevated liver malonaldehyde level resulting in hepatotoxicity (Lin et al., 1996). Treatment of rats with Hg showed significant increase in liver enzymes and damage of liver cells (Sener et al., 2007). Previous studies have revealed that HgCl₂ caused histopathological and ultrastructural lesions in the liver evidenced by fatty degeneration and cell necrosis (El-Shenawy and Hassan, 2008).

Spirulina platensis (SP) now named *Arthrospira*, is a filamentous cyanobacterium (blue green alga) that has a long history for use as food. It is rich in proteins, lipids, carbohydrates and some vital elements like zinc, magnesium, manganese, selenium, β-carotene, riboflavin, tocopherol and α-linoleic acid (Cohen, 1997). The antioxidant properties of *spirulina* and its capacity to scavenge hydroxyl radicals (Peter, 2008) and to inhibit lipid peroxidation (Karadeniz et al., 2008) have attracted

*Corresponding author. E-mail: Bashandys@hotmail.com. Tel: 0551902466. Fax: 0966-4678514.

the attention of many researches. *Spirulina* species exhibited various biological activities such as antihypertensive and antihyperlipemic (Torres-Duran, et al., 2007), Chemopreventive of cancer (Ismail et al., 2009) and hepatoprotective against cadmium toxicity (Karadeniz et al., 2009). These activities were largely related to phycocyanin, an active protein of *Spirulina* (Romay et al., 1998). Moreover, *Spirulina fusiformis* provides protection against mercuric chloride induced oxidative stress (Sharma et al., 2007).

Keeping in view the pharmacological properties of SP and its hypocholesterolemic effect in rabbit fed with diet rich in cholesterol (Colla et al., 2008), the present investigation was undertaken to assess the protective effect of SP against mercuric chloride induced hepatic toxicity and lipid profile alterations in male rats .

MATERIALS AND METHODS

Animals

Male wister albino rats, between 180 to 200 g, were obtained from the animal house, Faculty of Pharmacy, King Saud University, Riyadh. The animals were housed throughout the experiment in polypropylene cages (eight animals housed per cage) and allowed to acclimatize to laboratory environment for seven days before the beginning of the experiments. Animals were maintained under controlled conditions of temperature ($23\pm 1^\circ\text{C}$), humidity ($50\pm 15\%$) and normal photoperiod (12 to 12 h light-dark cycles). The animals were allowed free access to standard dry pellet diet and water ad libitum. This study was conducted in the Zoology Department, Faculty of Science, King Saud University, Saudi Arabia. The care and handling of experimental animals were carried out according to the animal ethical committee of King Saud University, College of Pharmacy.

Test chemicals

Mercury in the form of HgCl_2 was purchased from Merk, Germany, while *S. platensis* was obtained from Alibaba Company, China in form of tablets. 5-5-dithio-bis(2-nitrobenzoic acid) (DTNB), thiobarbituric acid and reduced glutathione was purchased from Sigma Company, USA.

Treatments

The animals were divided into four groups, each group containing eight rats. Animals in group 1 were used as control group and no treatment was given to these rats. Animals in group 2 were given *spirulina* daily by gavage for 60 consecutive days at dose level of 300 mg/kg dissolved in water (Simsek et al., 2009). Group 3 was injected (subcutaneous) with 5 mg/kg HgCl_2 dissolved in water three times weekly for 60 days. Animals in group 4 were given *Spirulina* (300 mg/kg) by gavage for 10 consecutive days before mercuric chloride administration and continued up to 60 days after mercuric chloride treatment.

Collection of samples

At the end of the experimentation period, blood was drawn from the animals by puncturing retro-orbital venous sinus, whole blood was used for determination of hydroperoxide level, while separated

plasma was used to determine liver enzymes, total protein and lipid profile. After blood samples collection, the animals from all groups were autopsied under light ether anesthesia. Liver was removed, rinsed in cold saline and processed for histological study and determination of MAD or GSH.

Biochemical studies

Determination of lipid peroxide levels

Blood hydroperoxide level was evaluated using an analytical system (Iram, Parma, Italy). The test is a colorimetric test that takes advantage of the ability of hydroperoxide to generate free radicals after reacting with transitional metals, when buffered chromogenic substance is added, a colored complex appears. This complex was measured spectrophotometrically.

Lipid peroxidation level in the liver was measured by method of Ohkawa et al. (1979) as thiobarbituric acid reactive substances (TBARS). Liver was homogenized in ice cold 0.15 M KCl (10%) and the concentration of TBARS was expressed as ng of malondialdehyde per g tissue using 1,1,3,3-tetramethoxypropane as standard. The absorbance was read at 532 nm.

Determination of hepatic glutathione

Glutathione level as reduced form was determined using 5-5-dithio-bis (2-nitrobenzoic acid) (DTNB) as a colouring reagent, following the method described by Moron et al. (1979). The absorbance was read at 412 nm by spectrophotometer. GSH concentration was calculated from a standard curve.

Determination of liver enzymes and lipid profile

Plasma AST, ALT and ALP were determined kinetically. Cholesterol, triglycerides, LDL, HDL and total protein, were evaluated colorimetrically in blood using kits from Bio Merieux, France. The intensity of the coloration was measured by using spectrophotometer, UV/visible-Model- 80-2106-00, Pharmacia Biotech. Cambridge, England.

Histopathological study

Small liver specimens were placed in 10% formol saline and processed routinely by embedding in paraffin. Sections (5 μm) of liver were stained with hematoxylin and eosin and examined under a light microscope.

Statistical analysis

All values were expressed as mean \pm S.E. Statistical analysis of data was performed using a student t-test.

RESULTS

Biochemical studies

Lipid peroxide levels

There was a significant decrease ($P < 0.01$) in the levels of blood hydroperoxide and hepatic MDA (Table 1) in

Table 1. Effect of *Spirulina* on lipid peroxidation products and hepatic glutathione content in rats treated with HgCl₂.

Parameters	Groups			
	Control	Spirulina	HgCl ₂	Spirulina+HgCl ₂
Blood hydroperoxide level (mg/100 ml)	28.42±0.63	24.11±0.32**	61.23±4.15**	45.96 ±2.89**b
Hepatic MDA content (ng/g tissue)	86.56±3.62	70.50±1.18**	195.62±9.78**	118.34 ± 5.46**b
Hepatic Glutathione content (µg/mg tissue)	16.68±0.42	17.64±0.57	9.36±0.25**	13.86±0.39**b

Each value is the mean ± S.E., n = 8. Values marked with asterisks differ significantly from control value: P<0.01, those marked with letter differ significantly from HgCl₂ group : P<0.01.

Table 2. Effect of *Spirulina* on the activity of plasma liver enzymes and protein concentration in rats treated with HgCl₂.

Parameters	Groups			
	Control	Spirulina	HgCl ₂	Spirulina+HgCl ₂
AST (U/L)	49.77±1.95	47.80±2.71	153.02±10.86**	103.54±3.60 **b
ALT (U/L)	23.22±1.52	25.32±1.66	41.07±3.98**	22.70±1.90 b
ALP (U/L)	245.69±7.26	240.35±9.84	298.78±11.61**	260.10±14.16
Total protein (g/100 ml)	7.62±0.37	7.85±0.23	5.74±0.33**	8.34±0.63 b

Each value is the mean ± S.E., n = 8. Values marked with asterisks differ significantly from control value : P<0.01, those marked with letter differ significantly from HgCl₂ group: P<0.01.

Table 3. Effect of *Spirulina* on plasma lipid profile in rats treated with HgCl₂.

Parameters (mg/100 ml)	Groups			
	Control	Spirulina	HgCl ₂	Spirulina+HgCl ₂
Cholesterol	72.14±3.34	65.46±2.70	90.80±4.36 **	70.26±2.43 b
Triglycerides	61.66±1.15	62.83±3.91	179.82±10.41**	116.56±8.16 **b
HDL-C	32.90±2.01	41.73±2.18**	22.61±0.32**	32.78±1.62 b
LDL-C	25.34±1.62	24.92±2.00	88.25±5.22**	50.47±2.66 **b

Each value is the mean ± S.E., n = 8. Values marked with asterisks differ significantly from control value: P<0.01, those marked with letter differ significantly from HgCl₂ group: P<0.01.

spirulina treated animals (Group 2). Mercuric chloride administration significantly (P<0.01) elevated the levels of hydroperoxide by 2.15 times and MAD by 2.26 folds with respect to control values. The two peroxide levels also increased significantly (P<0.01) in the combined treatment of SP with HgCl₂ by 1.60 and 1.4 fold compared to the control values. Moreover, the hydroperoxide or MAD level of SP+Hg group was significantly (P<0.01) lower than that of Hg group.

Hepatic glutathione content

There is no significant change in hepatic GSH content between *Spirulina* and control groups (Table 1). GSH level decreased significantly following HgCl₂ treatment (P<0.01) by 44% in respect to the control value. Although GSH level decreased significantly (P<0.01) in SP+Hg

group by 17%, its mean values were significantly (P<0.01) more than those of Hg group.

Liver enzymes and protein levels

Spirulina treatment has no significant influence on liver enzymes and protein levels. HgCl₂ intoxication causes a significant elevation of AST, ALT and ALP activities (P<0.01) by 3.07, 1.77 and 1.22 times respectively with respect to the control values (Table 2). On the other hand, AST activity of SP+Hg group increased significantly (P<0.01) by 2.08 fold, while ALT and ALP activities did not change significantly.

Protein values of Hg group were found to be significantly less (P<0.01) than those of control group. On the other hand, the protein value of SP+Hg group did not change significantly compared to control group, but still

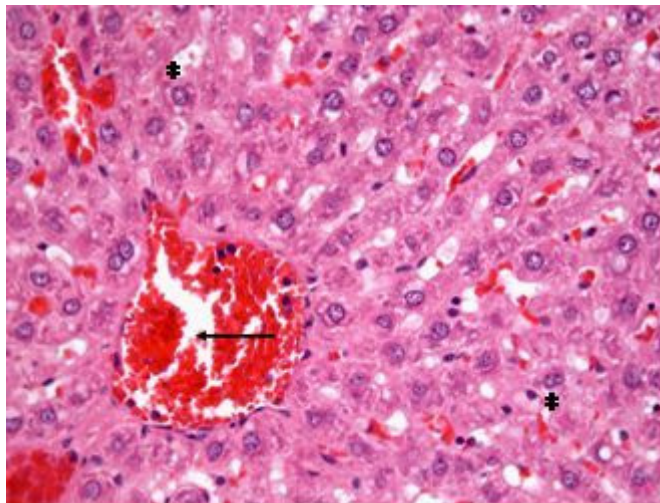


Figure 2. Liver tissue of HgCl₂- treated rats showing haemorrhage in the central vein (←), necrosis; (*), HE, X 400.

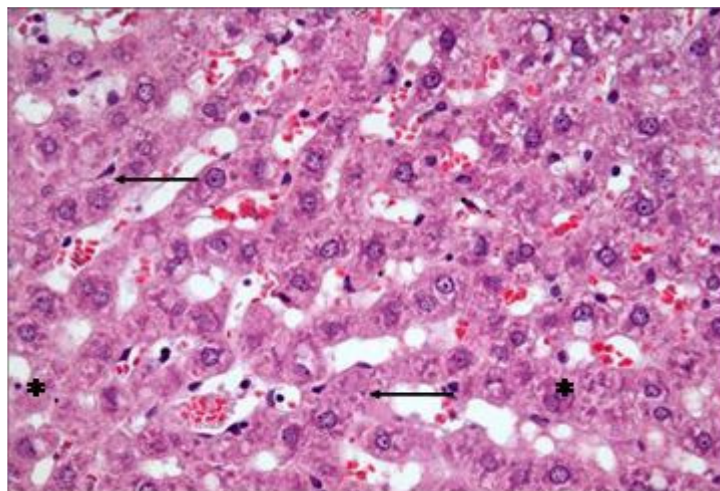


Figure 2. Liver tissue of HgCl₂- treated rats showing dilation of blood sinusoids (←), and necrosis (*). HE, X 400.

significantly ($P < 0.01$) higher than that of Hg group.

Lipid profile

Spirulina treatment significantly elevated plasma HDL-C level but did not significantly change cholesterol, triglycerides and LDL-C levels in respect to control values (Table 3). The treatment of animals with HgCl₂ induced a significant increase ($P < 0.01$) in cholesterol, triglycerides and LDL-C levels and a significant decrease in HDL-C level. Animals treated with *Spirulina* plus Hg showed a significant ($P < 0.01$) increase in triglycerides and LDL-C levels as compared to control, whereas no significant differences were found in other tested lipid profile

parameters. However, the levels of both triglycerides and LDL-C in SP+Hg group were significantly less than those of Hg group.

Histopathological study

Mercuric chloride induces various pathological alterations in liver of albino rats. These alterations were characterized by dilatation, of central vein with hemorrhage (Figure 1). Moreover, dilatation of blood sinusoids and necrosis of hepatocytes were observed in liver sections of Hg-group (Figure 2) compared with control (Figure 3). In the combination group, liver showed less histopathological changes (Figure 4).

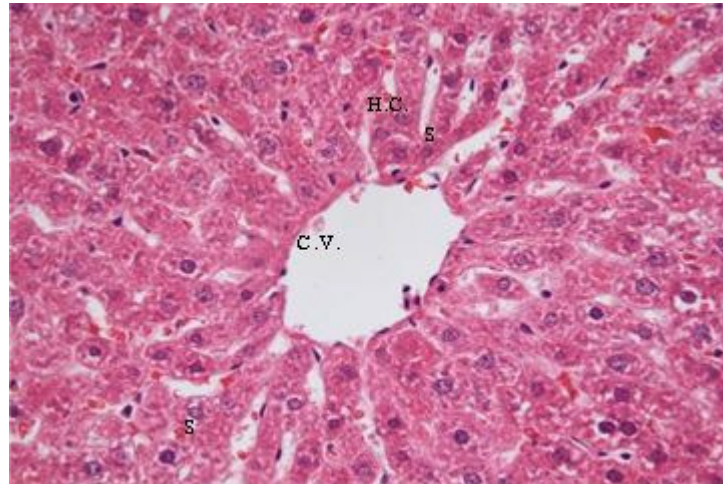


Figure 3. Liver tissue of control showing normal structure, central vein (C.V.), normal arrangement of hepatic cords (H.C.), normal blood sinusoids (S) and hepatocytes. HE, X 400.

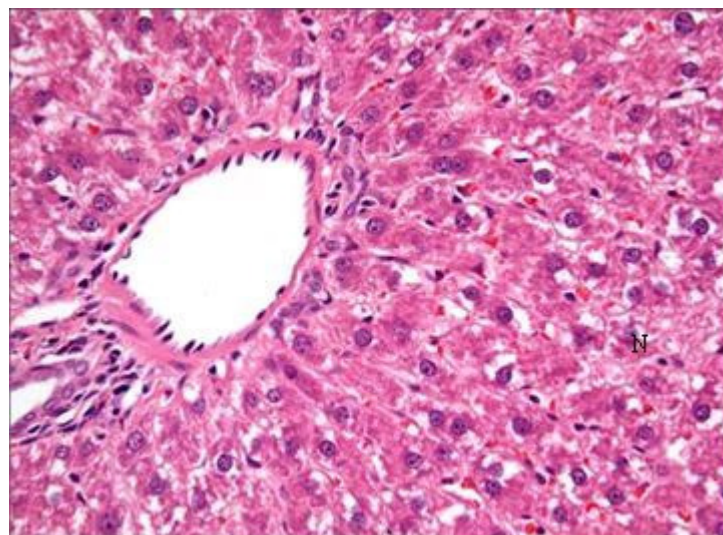


Figure 4. Liver tissue of spirulina-treated rats showing few necrosis (N). HE, X 400.

DISCUSSION

Mercury can cause biochemical damage to tissues through diverse mechanisms including enhancement of lipid peroxidation (LPO) and reduction of antioxidant enzymes (Rao and Chhunchha, 2009). The present investigation revealed that mercuric chloride intoxication causes a significant increase in lipid hydroperoxide and hepatic MDA levels which are the major primary products of free radical mediated LPO of polyunsaturated fatty acids. The observed increase in peroxide levels in rats treated with HgCl_2 may indicate oxidative stress which affects liver organelles. Lipid peroxides that accumulate

due to peroxidation of lipids are known to be harmful to cells and tissues (Linden et al., 2008). The observed histopathological changes in the liver of HgCl_2 intoxicated rats may be due to increased levels of peroxide.

In the present investigation, the administration of *Spirulina* to rats given HgCl_2 reduced the elevation of peroxide levels which may indicate that *Spirulina* reduce the oxidative stress produced by mercury via its antioxidant components, phycocyanin and β -carotene (Guan et al., 2009, Luxia, et al., 1996), or via reduction of lipid peroxidation (Karadeniz et al., 2008). β -carotene of *Spirulina* may scavenge free radicals generated by mercuric chloride and reduces lipid peroxidation.

Our study demonstrates that the treatment of rats with HgCl_2 decreased hepatic GSH level significantly. The principal toxic effects of mercury involve interactions with a large number of cellular processes, including formation of complexes with free thiol groups, which may lead to oxidative stress (Stacey and Kappus, 1982). Glutathione, as both carrier of mercury and an antioxidant, has specific roles in protecting the body from mercury toxicity. GSH binds with mercury, forms a complex that prevents mercury from binding to cellular proteins and causing damage to both enzymes and tissue (Kromidas, et al., 1990). As a result of binding of mercury to glutathione and subsequent elimination of intracellular glutathione, levels of GSH are lowered in the cell and decrease the antioxidant potential of the cell. In the present study, *Spirulina* alleviated the decrease in GSH content of the liver due to Hg treatment. It appears that *Spirulina* exerts its protective effect against mercury directly through its antioxidant properties or indirectly through maintaining the hepatic GSH.

The relation between the hepatic tissue damage and elevation of the relevant serum enzymes is well documented (Dhu et al., 2004). The observed increase in the activities of plasma AST and ALT of HgCl_2 intoxicated rats is likely due to lipid peroxidation of biomembranes which cause leakage of cellular components (Matsuo et al., 1989). This confirms our reports on histopathological alterations in the liver induced by mercury. These results are in agreement with Zhao et al. (2009), who mentioned that mercury intoxication produced significant hepatic damage as evidenced by increase in the leakage of AST, ALT. The increase in plasma level of ALP is perhaps due to increased synthesis of ALP and amplified biliary pressure (Kumar et al., 2005). Currently, injection of rats with HgCl_2 led to a significant decrease in plasma protein level. The decrease in protein level may be due to inhibition of amino acid transporter (Brookes and Kristt, 1989) or RNA synthesis (Sarafian and Verity, 1983).

In the present study, the rats given *Spirulina* with HgCl_2 showed a significant improvement of elevated plasma enzymes levels indicative of liver function as compared with HgCl_2 group. Moreover, the concentration of protein in *Spirulina*+ HgCl_2 group is about normal values. Some of the active constituents of *Spirulina* have been reported to possess strong antioxidant activity and provokes free radical scavenging enzyme system. The protective role of *Spirulina* may be attributed to the presence of β -carotene (Luxia et al., 1996), enzyme superoxide dismutase or selenium (Henrikson, 1989) and blue pigment phycocyanin (Bhat and Madyastha, 2001). Luxia et al. (1996) reported that β -carotene of *Spirulina* may reduce cell damage, especially the damage to DNA molecules, thus playing the role in the repair of regeneration process of damaged liver cells.

Furthermore, since tissue damage causes functional impairments in Hg treated group, elevation of peroxides level cause a significant increase in liver function tests.

Our results showed that *Spirulina* treated significantly inhibits peroxides production, implying a reduction in lipid peroxidation and cellular injury that protect the liver against Hg-induced oxidative damage. Accordingly functional parameters were also improved.

Mercury has been shown to promote atherosclerosis (Skoczynska et al., 2009). The present investigation demonstrates that HgCl_2 induced significant elevation of cholesterol, triglycerides and LDL-C. Moreover, HDL-C level decreased significantly in Hg group. The increased level of LDL-C and decreased HDL-C in Hg group reflected the abnormalities in lipoprotein metabolism which may result in high level of cholesterol and development of atherosclerosis.

In our study, cholesterol, triglycerides and LDL-C of *Spirulina*+Hg group showed a significant reduction as compared with Hg group with an increase in HDL-C concentration. The hypocholesterolemic effect of *Spirulina* in rabbits fed on diet enriched with cholesterol (Colla et al., 2008) has also been reported. It was observed that *Spirulina* decreased plasma cholesterol level and increased HDL-C suggesting that *Spirulina* could have protective effect on the cardiovascular system (Ray, 1991). According to Hill and McQueen (1997), HDL-C has known to be protective against the development of atherosclerosis. There is an inverse relationship between HDL-C concentration and the incidence of coronary heart disease. HDL reverse cholesterol transport whereby cholesterol synthesized is returned to the liver for reuse or re-excretion into the bile resulting in a decrease of cholesterol level. The present study demonstrates a reduction in atherogenic indices LDL-C/HDL-C and TC/HDL-C of *Spirulina*+Hg group. This may indicate the protective effect of *Spirulina* against cardiovascular diseases induced by mercury. The hypotriglyceridemic effect of *Spirulina* may be through its effect on increase the activity of lipase (Iwata et al., 1990). The presence of antioxidant compounds like phycocyanin and β -carotene, linolenic acid and sulfated polysaccharide in *S. platensis* can be the cause of the properties of *Spirulina* on the decrease of plasma lipids levels. According to Nagaoka et al. (2005), phycocyanin caused hypocholesterolemic activity in rats. They hypothesized that phycocyanin binds to bile acids in the jejunum, this binding affects the micellar solubility of cholesterol and then suppresses cholesterol absorption. Seo et al. (2004) reported that β -carotene reduced the elevation of cholesterol and triglycerides of diabetic rats. Both sulfated polysaccharides and linolenic acid showed hypolipidemic effect (Godard et al., 2009; Serougne et al., 2004). Moreover, Kim et al. (2004) found that feeding of rats with linolenic acid rich oil lowers plasma triacylglycerol and inhibits hepatic fatty acid synthesis which may result in a hypolipidemic effect.

The present study demonstrates that the increase in lipid peroxide levels responsible for Hg-induced hepatotoxicity alleviated by *Spirulina* which in turn is reflected by improvement of several biochemical parameters and

reduction of histopathological changes of liver. The hepatoprotective of *S. platensis* may be due to its active principles which showed antioxidant activities. Also, it could be concluded that *Spirulina* showed hypolipidemic effect in Hg-treated rats with an increase in the plasma level of HDL-C and decrease of atherogenic indices. Hence, *S. platensis* can be considered a protective agent against the development of atherosclerosis and hepatotoxicity induced by mercury.

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