

BIOLOGICAL EFFECTS OF *Spirulina* AND CURRENT RESEARCH ON ITS ANTIOXIDANT ACTIVITY

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The most prevalent diseases around the world are obesity, type 2 diabetes mellitus, and hypertension. Insulin resistance is common among them, and it is present during some phases of their evolution. Other diseases grouped as “Non-Alcoholic Fatty Liver Disease”, share insulin resistance as a pathogenic mechanism.

Spirulina is a filamentous cyanobacterium used as a food supplement because of its high nutrient content. It has been experimentally proven, *in vivo* and *in vitro*, that it possesses several pharmacological properties such as antiviral effects, anti-cancer properties, and anti-inflammatory effects. *Spirulina* has also shown effects on regulating the lipid and carbohydrate metabolism, as evidenced by its hypocholesterolemic, hypoglycemic, and antihypertensive effects.

Previous studies in our laboratory have demonstrated the hepatoprotective effects of *Spirulina maxima* against the damage produced by carbon tetrachloride. In these studies, a 5% *Spirulina maxima* supplemented diet decreased serum aspartate aminotransferase, liver triacylglycerols, cholesterol, free fatty acids, and thiobarbituric acid reactive substances. The exact mechanism by which it exerts those effects is not well known, but some antioxidant effects have been observed in the presence of *Spirulina*. The purpose of this review is to summarize the current biological effects of this cyanobacterium, particularly on the antioxidant enzyme system. In our perspective, *Spirulina maxima* and *platensis* could be useful as a dietary supplement for the treatment of patients with obesity-related pathologies such as hypertension, diabetes mellitus, dyslipidemia, and non-alcoholic fatty liver disease.

Palabras clave: *Arthrospira*, antioxidant, Non-Alcoholic Fatty Liver Disease

Las enfermedades más prevalentes en todo el mundo son la obesidad, diabetes mellitus tipo 2 e hipertensión. La resistencia a la insulina es común entre ellas, y está presente en algunas fases de su evolución. Otras enfermedades agrupadas bajo el término de hígado graso no alcohólico, comparten la resistencia a la insulina como mecanismo patogénico.

La *Spirulina* es una cianobacteria filamentosa utilizada como suplemento alimenticio por su alto contenido de nutrientes. Se ha comprobado a nivel experimental, *in vivo* e *in vitro*, que posee varias propiedades farmacológicas tales como efectos antivirales, propiedades anti-cáncer, y efectos anti-inflamatorios. La *Spirulina* también ha mostrado efectos en la regulación del metabolismo de lípidos y carbohidratos, como se ha demostrado por sus efectos hipocolesterolémico, hipoglucemiante y antihipertensivo.

Estudios previos realizados en nuestro laboratorio han demostrado los efectos hepatoprotectores de *Spirulina maxima* contra el daño producido por el tetracloruro de carbono. En dichos estudios, una dieta suplementada con 5% de *Spirulina maxima* disminuyó en plasma la aspartato aminotransferasa, y en hígado los triacilglicérols, el colesterol, los ácidos grasos libres, y las sustancias reactivas al ácido

tiobarbitúrico. Los mecanismos precisos para explicar esos efectos no se han esclarecido, pero se han observado algunos efectos antioxidantes en presencia de *Spirulina*. El propósito de esta revisión es resumir los efectos biológicos actuales de esta cianobacteria, en particular en el sistema de enzimas antioxidantes. Desde nuestra perspectiva, *Spirulina maxima* y *platensis* podría ser útiles como suplemento dietético para el tratamiento de pacientes con patologías relacionadas con la obesidad, como la hipertensión, la diabetes mellitus, la dislipidemia y la enfermedad de hígado graso no alcohólico.

Index words: *Arthrospira*, antioxidante, hígado graso no alcohólico

Recibido: Junio 6 de 2011. Aceptado: Julio 22 de 2011

BACKGROUND

Living organisms face diverse attacks from the environment that affect oxide-reduction cellular homeostasis, influencing the balance between pro-oxidants and antioxidants. During these states, high-reactivity and great-unstable intermediate metabolites derived from the incomplete reduction of oxygen (ROS, reactive oxygen species) or nitrogen (RNS, reactive nitrogen species) take place (grouped as RS); they are also called free radicals that produce cellular damage in biological systems induced by chain reactions. In fact, there are many factors that induce the RS to release, like inflammatory process, ischemic-reperfusion injury, septic shock, autoimmune diseases, pollution, aging, excessive exercise, undernourishment, obesity, and certain drugs (1).

Mates *et al.* (1) described that RS are involved in the pathogenesis of human diseases such as allergic processes (e.g., intolerance to aspirin), cancer (bladder, breast, colorectal, kidney, liver, skin, or leukemia), atherosclerosis, damage from mechanisms of certain microorganisms (hepatitis, *H. pylori* infection, HIV, *Influeza* virus), genetic disorders (chronic granulomatous disease, Down's syndrome), metabolic disturbance (diabetes mellitus), and neurodegenerative pathologies (allergic encephalomyelitis, Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease).

Liver diseases show a growing incidence in Mexico (2); almost half of them are produced by alcohol consumption, and some are included in the so-called Non-Alcoholic Fatty Liver Disease (NAFLD). The NAFLD is a risk factor for

cirrhosis and liver cancer in almost 33% and 25% of these cases, respectively (3). It is well known that RS are involved in their physiopathology (4). According to the "two hits theory", the liver is exposed to the first hit, consisting of an increased fatty acid flux to mitochondria, and its incorporation into triacylglycerols (TAG), phospholipids, and cholesterol esters (this process explains NAFLD induced by obesity, a rich caloric diet, or after bypass surgery). The second hit is where these compounds are more susceptible to oxidative stress, increasing secretion of cytokines involved in fibrogenesis (5).

Fortunately, antioxidant systems (both enzymatic and non-enzymatic) eliminate these RS, especially those generated by the mitochondrial respiratory chain in oxidative phosphorylation. Non-enzymatic defenses include glutathione, uric acid, bilirubin, and vitamins like C and E; whereas enzymatic defenses include superoxide dismutase (SOD), catalase (CAT), and the glutathione system (Glutathione S-transferase, reductase, and peroxidase) (6).

Current NAFLD treatment approaches include antioxidant agents like vitamin E, betaine, or N-Acetyl-cysteine. Some natural products with high contents of these antioxidants have been used as supplements in treatments for NAFLD and obesity-related diseases.

It has been demonstrated that *Spirulina* protects against liver damage induced in rats by an intraperitoneal dose of 2mL/kg carbon tetrachloride (CCl₄). A diet supplemented with 5% *Spirulina maxima* prevented the CCl₄-induced increase of serum aspartate

aminotransferase, liver TAG, liver total cholesterol (TC), liver free fatty acids (with an important decrease of unsaturated fatty acids), and thiobarbituric acid reactive substances (TBARS, which are indicators for lipoperoxidation) (7). On the other hand, 4.5 g/day of *Spirulina maxima* consumption attenuates liver damage in humans as evidenced by ultrasonography and aminotransferase data (8).

General aspects of *Spirulina*

Spirulina, a filamentous and unicellular alga is a cyanobacterium belonging to the Oscillatoraceae family that usually grows in the alkaline waters of Africa, Asia, North and South America. In addition, it is generally cultured in semi-desert areas during almost all the year. Each cell has a diameter of 5 to 10 µm, with a helical and filamentous form and 5 or 6 turns. It is characterized by helical diameter of 50 to 60 µm and 200 to 300 µm long.

Three species of *Spirulina*, including *Spirulina platensis*, *Spirulina maxima*, and *Spirulina fusiformis* are the most investigated because of their high nutritional values, namely, 60% dry weight as protein, contains all essential aminoacids and essential fatty acids, high content of B complex vitamins, as well as selenium, tocopherol and other antioxidants (9, 10). Because of the above mentioned, the Food and Drug Administration (FDA) recognize to the *Spirulina* as a GRAS product (Generally Recognized as Safe).

At the pre-Colombian America, *Spirulina maxima* was used like food and was called "tecuitlatl" by ancient Aztecs, who harvested in the Texcoco lake. Furthermore, *Spirulina platensis* usually grows in Chad Lake, and it is consumed by local inhabitants. Nowadays, *Spirulina* is consumed by athletes, vegetarians, malnourished, among others, due to their nutritional and therapeutic properties (11). The purpose of this review is to summarize available information on the antioxidant effects of *Spirulina* related liver protection.

Biological effects of *Spirulina*

Some of its properties include prevention of anemia because of high iron and vitamin contents (12), inhibition of herpes simplex infection (13), decrease in HIV replication velocity (14), increased production of antibodies, anti-inflammatory properties, prevention of proliferation of neoplastic cells (15), hypoglycemic (16), hypolipemic (17) and antihypertensive properties in experimental animal models and humans (18), as well as hepatoprotective properties through decreasing of the liver lipid profiles and lipoperoxidation products (19). Nevertheless, its mechanisms for tissue protection and certain biological effects are not fully understood. Certain compounds like Calcium spirulan (Ca-Sp), a sulfated polysaccharide isolated from *Spirulina platensis* has antiviral activity in cultured human fetal lung fibroblasts (20). Additionally, Ca-Sp acts on thrombin inhibition, interacting with heparin cofactor II. Majdoub *et al.*, (21) isolated crude polysaccharide extracts by ultrafiltration (named as PUF1 and PUF2) and found that PUF2 had an effective anticoagulant activity. Moreover, it is well known that *Spirulina maxima* is a rich source in C-phycoerythrin, a compound associated with antioxidant properties like a free radical scavenger (22). Furthermore, Hsiao *et al.*, (23) proposed that this compound inhibits platelet aggregation through inhibition of calcium mobilization and mediation of free radicals released by platelets. Nagakoa *et al.*, (24) also found that it inhibits jejunal cholesterol absorption and ileal bile acid reabsorption. In a recent study, Vázquez-Sánchez *et al.*, found that an active protein extract (SPE) isolated from *S. maxima* protects against teratogenesis induced by hydroxyurea in mice (25).

Other compounds obtained from *Spirulina*, like sulpholipids, Cyanovinin-N, and certain vitamins and essential fatty acids, have been related with beneficial effects on hematopoiesis, obesity, and neurological disorders (Figure 1). Recently described effects of *Spirulina fusiformis* and *Spirulina platensis* are summarized in Table 1.

Table 1. Effects of *Spirulina platensis* and *fusiformis*.

Specie	Model	Doses	Effect	Reference
<i>Spirulina platensis</i>	Humans	7.5 g/day/3 weeks	Prevents effect of skeletal muscle damage and put off time of exhaustion during exercise	Lu H.K. (26)
	Humans	4.2 g/day/8 weeks	Helps to reduce increased levels of lipids in patients with hyperlipidemic nephrotic syndrome	Samuels R. (27)
	Rats	100-1000 µg/g b.wt	Inhibits mast cell-mediated immediate-type allergic reactions <i>in vivo</i> and <i>in vitro</i>	Kim H.M. (28)
	Rats	300 mg/kg	Adjuvant in treatment of leukemia and anemia caused by lead and cadmium intoxication	Simsek N. (29)
	Rats	400 mg/kg	Normalizes changes observed in arthritic rats to near normal conditions	Kumar N. (30)
	Rats	1000 mg/kg orally	Protects against gentamicin-induced nephrotoxicity	Karadeniz A. (31)
	Rats	300 mg/kg	Protects against cadmium induced oxidative stress	Karadeniz A. (32)
	Rats	Diet supplemented with <i>S. platensis</i> 1%	Chemoprotective effect against dibutyl nitrosamine (DBN) Decreases histopathological changes induced by DBN	Ismail M.F. (33)
	HepG2 cells (<i>in vitro</i>)	200 µg/mL	Induces p53 with subsequent up-regulation on cell cycle inhibitor p21	
	<i>In vitro</i>	Crude polysaccharidic fraction extracted by ultrafiltration	PUF2 compound showed higher anticoagulant activity than dermatan sulfate	Majdoub H. (21)
Rats	1000 mg/kg orally	Lower renal damage induced by nitrites in rats with renal injury caused by gentamicin	Advagic N. (34)	
<i>Spirulina fusiformis</i>	Rats	500, 1000, 1500 mg/kg	Potential beneficial effects on nephrotoxicity induced by cisplatin	Kuhad A. (35)
	Mice	800 mg/kg b.wt	Modifies renal damage against mercuric chloride-induced toxicity	Sharma M.K. (36)
	Mice	800 mg/kg b.wt	Modulates mercury-induced testicular toxicity	Saxena P.S. (37)
	Mice	800 mg/kg/b.wt	Anti-inflammatory activity against adjuvant-induced arthritis	Rasool M. (38)
	Mice	250-1000 mg/kg	Inhibits genotoxicity induced by cisplatin and urethane	Premkumar K. (15)

The biological effects of *Spirulina platensis* and *Spirulina fusiformis* are shown. The experimental model, dose of *Spirulina* used, and the main effects are summarized. For further information about the experimental conditions and the results, the references are included. - b.wt: body weight.

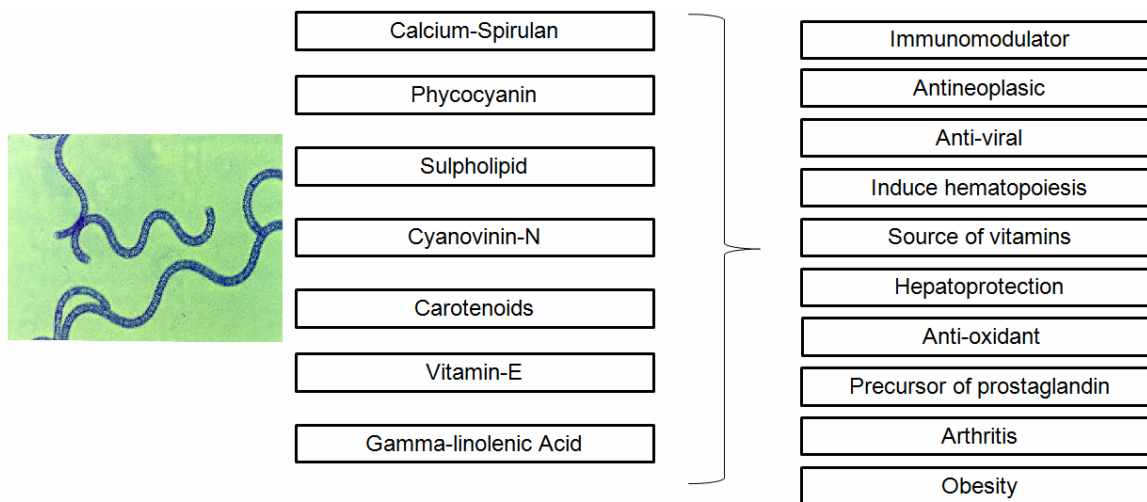


Figure 1. Biological effects of *Spirulina* and related compounds. Adapted from Khan *et al.* [9].

Spirulina and NAFLD

As mentioned before, in a model used in our laboratory, a single intraperitoneal dose of 2 mL/kg CCl₄ acts as a hepatotoxic that induces steatohepatitis. We found in rats that a commercial diet supplemented with 5% of *S. maxima* decreases serum triacylglycerols (26.4%), aspartate aminotransferases (54.1%), liver triacylglycerols (29.1%) at 48h post-treatment. The same pattern was observed for liver free fatty acids (61%) with an important decrease of unsaturated fatty acids (47.8%) and TBARS (51.9%) (7). These results suggest that *Spirulina* has hepatoprotective properties through decreasing the liver lipid profile and possess an antioxidant mechanism. In fact, a recent study in our laboratory showed the effects of 5% *S. maxima* diet on the antioxidant system in the hepato- and nephrotoxicity induced by lead acetate (three doses of 25mg i.p.) in male Wistar rats. We found a decrease in liver GSH content, CAT and SOD activities, and an increase on TBARS levels in rats exposed to lead in comparison with control group. In rats fed on *Spirulina* and exposed to lead, an increase on antioxidant enzyme activity and a decrease on TBARS levels were observed compared to rats without *Spirulina* feeding and exposed to lead in

both liver and kidney (Figures 2 and 3). We propose these effects could be related to the radical scavenging activity of *S. maxima* components (39). In addition, it has been demonstrated that *S. maxima* prevents development of the fatty liver induced in mice by simvastatin, ethanol, and a hypercholesterolemic diet (19).

In another study conducted in our laboratory, three patients, 40-60 years old, diagnosed with NAFLD by ultrasonography, consumed 4.5 g/day of *S. maxima* in tablet form (0.5g each). After three months of treatment, it was demonstrated an average decrease of 34-41% in their alanine aminotransferase (ALT) activity. Furthermore, there was a decrease in TAG, TC, cholesterol associated to low density lipoprotein (LDL-C), and total cholesterol/cholesterol associated to high density lipoprotein (CT/HDL-C) ratios with an average of 19%, 16%, 22%, and 18%, respectively. As seen in Figure 4, all cases showed a reduction in indicative characteristics of NAFLD in form of resolution of hyperechogenicity pattern (“brilliant liver”). Finally, we assessed parenchymal changes seen in all of them in ultrasonography (resolution of the so-called “brilliant liver” ultrasonographic pattern seen on NAFLD) (8).

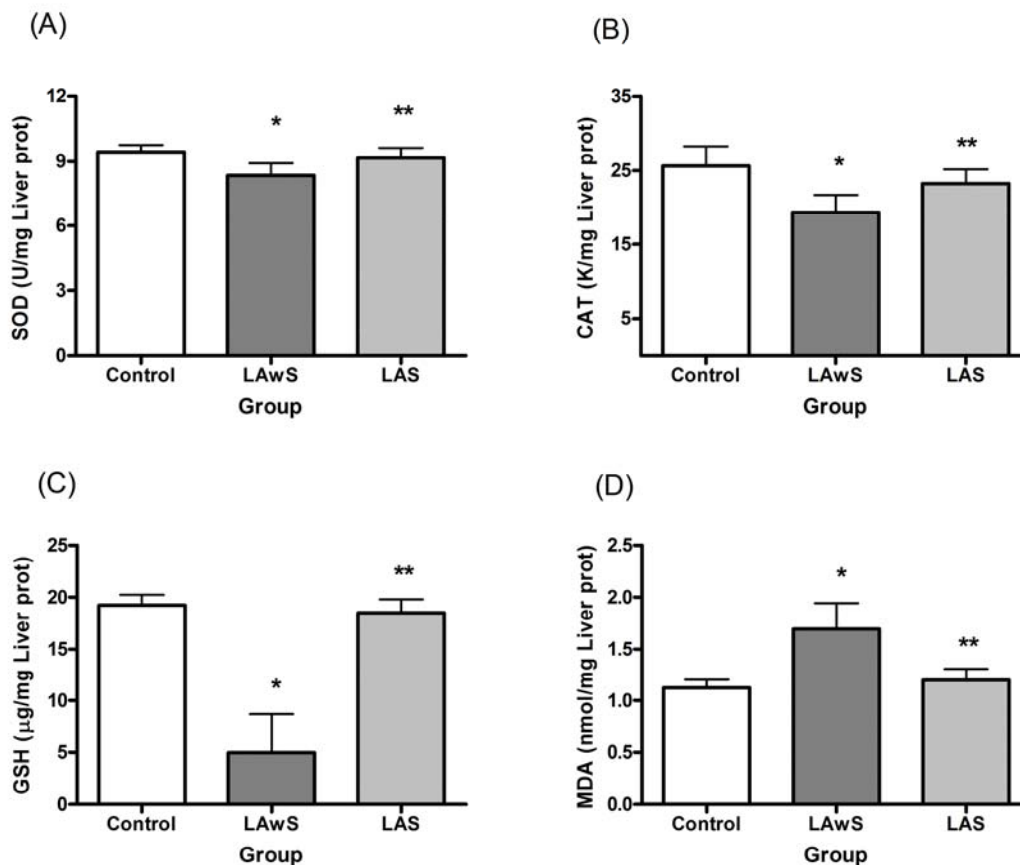


Figure 2. Effects of *Spirulina maxima* on liver oxidative status indicators during lead exposure in rats. The animals were treated with a vehicle or with 75 mg of lead acetate (LA, 25 mg/0.5 ml isotonic saline each, i.p., and three times on days 14, 21 and 28, an sacrificed on day 30). Values are expressed in mean \pm SD of n = 6 rats. (A). The total Superoxide Dismutase (SOD) activity. (B). The Catalase (CAT) activity. (C). The Glutathione (GSH) levels. (D). The Thiobarbituric Acid-Reactive Substances (TBARS) levels. Control (no LA and without *Spirulina*), LAwS (LA without *Spirulina*), LAS (LA with *Spirulina*). *p < 0.05, LAwS group compared with the Control group. ANOVA with Bonferroni test. **p < 0.05, LAwS group compared with the LAS group. ANOVA with Bonferroni test. Figure from Ponce-Canchihuamán *et al.* (39).

In vitro and in vivo evidence of Spirulina in oxidative stress

Bermejo-Bescos *et al.*, (40) assessed the protective effects of *Spirulina platensis* on antioxidant enzymes of glutathione in neuroblastoma SH-SY5Y cells. They observed that *Spirulina platensis* at 500 µg/mL restored the activities of glutathione reductase, and glutathione peroxidase-Se, as well as glutathione levels previously affected by iron insult (-28.6%, -50.5%, and -47.4%, respectively). On the other

hand, Thaakur and Sravanthi evaluated the neuroprotective effect of *Spirulina maxima* on male albino rats (41). The last authors induced cerebral ischemia-reperfusion injury and appreciated approximately a 50% decrease in SOD, CAT and glutathione levels and two-fold increase on TBARS level. Pretreatment with *Spirulina* (45-180 mg/kg) significantly reversed the decreased levels of those antioxidant components and reduced malonic dialdehyde (MDA) levels. Furthermore, they assessed by histopathological studies that *Spirulina* reversed

necrotic changes induced by ischemia. Another study, conducted in mice with cardiotoxicity induced by doxorubicin, demonstrated that pretreatment with *Spirulina* at a dose of 250 mg/kg, normalized the antioxidant enzyme levels (42). Other studies assessed that *Spirulina*

consumption restored the decreased levels induced by drugs like haloperidol, cisplatin, urethane, cadmium, gentamicine, and mercury; protecting against damage induced in the liver, brain, and kidney (see also Table 1).

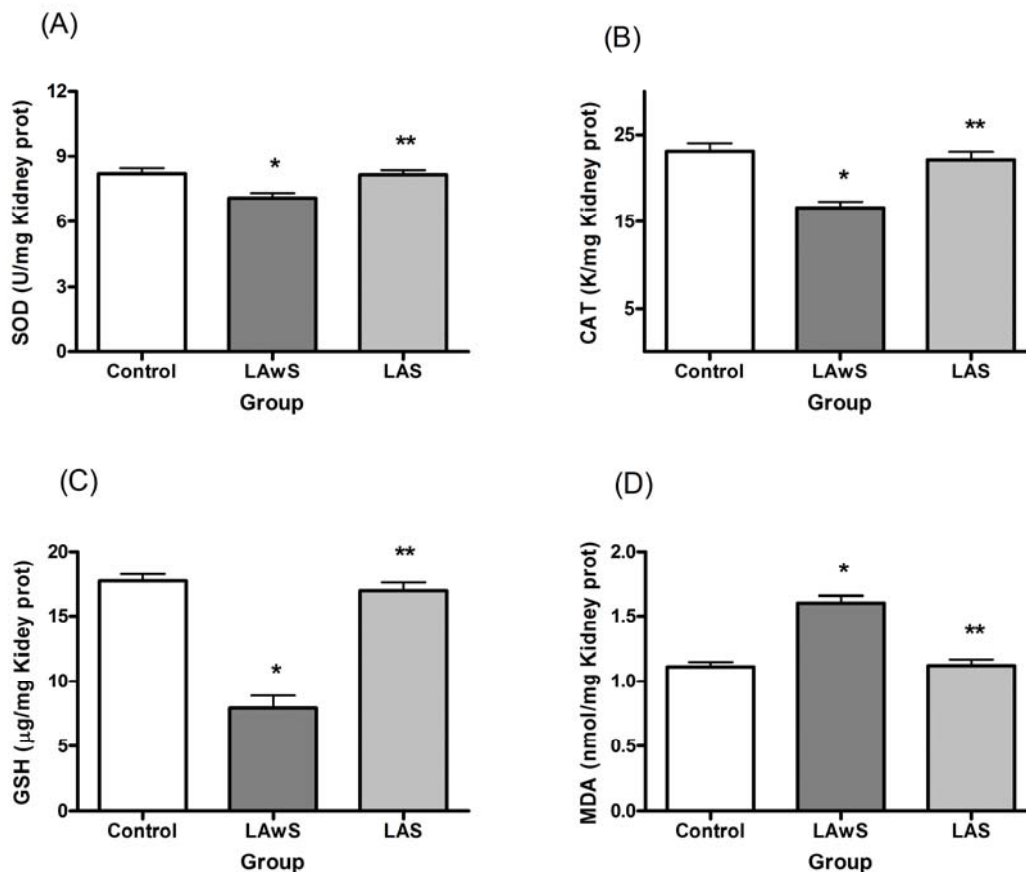


Figure 3. Effects of *Spirulina maxima* on kidney oxidative status indicators during lead exposure in rats. The animals were treated with a vehicle or with 75 mg of lead acetate (LA, 25 mg/0.5 ml isotonic saline each, i.p., and three times on days 14, 21 and 28, and sacrificed on day 30). Values are expressed in mean \pm SD of n = 6 rats. (A). The total Superoxide Dismutase (SOD) activity. (B). The Catalase (CAT) activity. (C). The Glutathione (GSH) levels. (D). The Thiobarbituric Acid-Reactive Substances (TBARS) levels. Control (no LA and without *Spirulina*), LAwS (LA without *Spirulina*), LAS (LA with *Spirulina*). *p < 0.05, LAwS group compared with the Control group. ANOVA with Bonferroni test. **p < 0.05, LAwS group compared with the LAS group. ANOVA with Bonferroni test. Figure from Ponce-Canchihuamán *et al.* (39)

Concerning to studies in humans, Lu *et al.* demonstrated that consumption of a diet containing 5% *Spirulina platensis* for 3 weeks. Blood samples were taken after finishing the Bruce incremental treadmill exercise before and

after treatment. The results showed that plasma concentrations of MDA were significantly decreased, and blood SOD activity was increased, after supplementation with *Spirulina* (26). Another report by Kalafati *et al.* assessed

the effects of *Spirulina* supplementation on the REDOX state and metabolic parameters related to exercise. For this purpose nine moderately trained men were fed a diet supplemented with *S. platensis* (6 g/day) versus a control group fed a placebo for 4 weeks. After an exercise with intensity on 70-75% VO_2max , exercise performance and antioxidant components like

GSH, oxidized glutathione (GSSG), GSH/GSSG, SOD, CAT, total antioxidant capacity (TAC), and TBARS were determined. This report demonstrates an improvement in time-to-fatigue after exercise, an increase in fat oxidation, and increase on GSH, TBARS and, TAC (43).



Figure 4. Ultrasonographic changes seen in patients treated with *Spirulina*. Before treatment, patients with NAFLD showed a pattern known as “brilliant liver”. After treatment with *Spirulina* we could observe a decrease on that pattern.

We are currently investigating the effects of *Spirulina platensis* on antioxidant systems and their possible correlation with hepatoprotective effects in a rat model using carbon tetrachloride. Carbon tetrachloride is a potent hepatotoxin that produces centrolobulillar necrosis through production of trichloromethyl radicals, a metabolite generated by CYP2E1 that induces lipoperoxidation (Figure 5). Our current protocol includes male Wistar rats fed for 15 days with a commercial diet (AIN-76, MP Biomedicals) compared with experimental groups fed with the same diet supplemented with 5% *S. platensis* in powder (20 g/day/rat) and tap water *ad libitum*. Using a sublethal dose of CCl_4 (2 mL/kg, i.p.) we have compared *Spirulina* effects on levels of TAG, TC and HDL-C, TBARS, SOD, CAT, and GSH in the serum and liver of control and

treated animals. Preliminary results have shown no changes in serum SOD or CAT activities. Nevertheless, we observed that CCl_4 induces a decrease in serum GSH levels, and an increase in serum TBARS levels compared to the control group; however, *Spirulina* administration attenuates these effects (Figure 6).

CONCLUSION

The changes seen on the antioxidant systems could explain some of the action mechanisms implicated in the biological effects of *Spirulina*. Some components of *Spirulina* have shown antioxidant effects, namely, phycocyanin, carotenoids, chlorophyll, selenium, gamma linolenic acid, tocopherol; however, it is likely

that the biological effects observed are due to joint action them. For all these reasons,

incorporating *Spirulina* in our diet can have beneficial health effects.

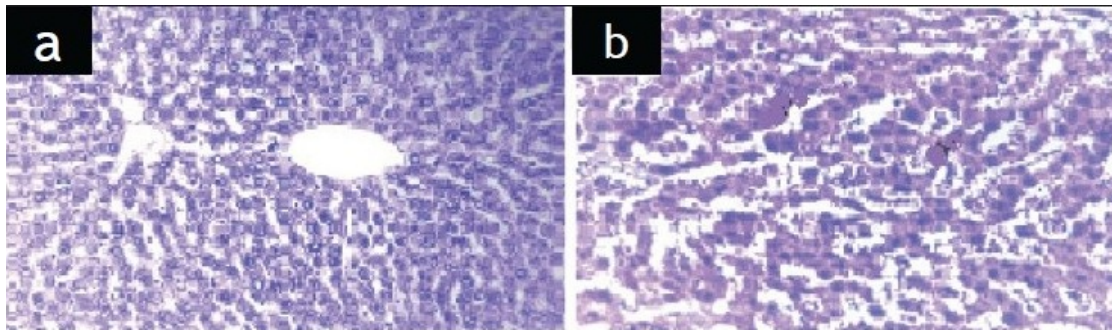


Figure 5. Photomicrographs of hepatocytes from normal and treated rat livers (a) liver of normal non treated rat showing normal histological picture, (b) liver of CCl₄-intoxicated rats showing severe centrilobular necrosis, degeneration in hepatocytes, congestion in the central vein and sinusoids, proliferation of Kupffer cells and mononuclear leucocytes inflammatory cells. Adapted from Atta *et al.* (44).

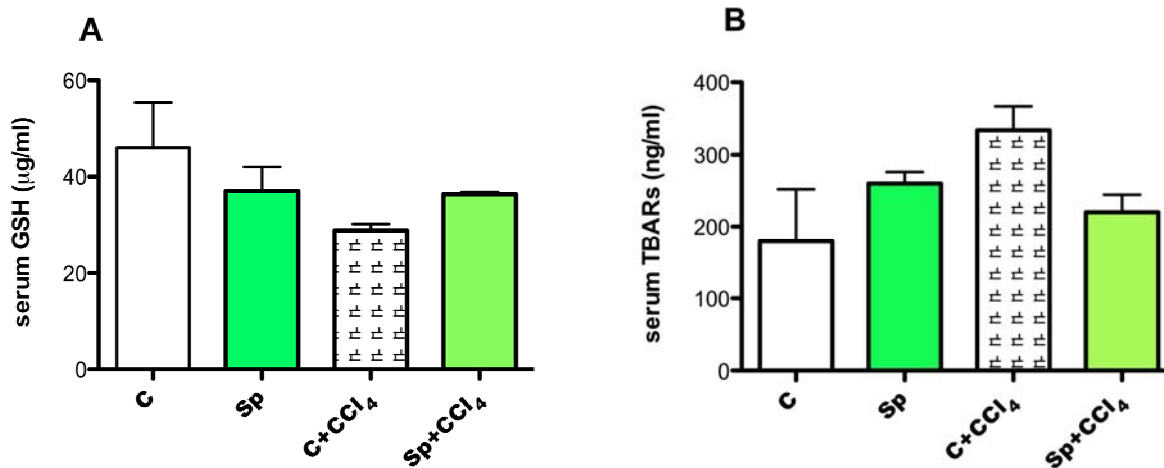


Figure 6. *Spirulina* effects on the serum GSH concentrations (A), and Serum TBARs concentrations (B). C = rats fed on commercial diet; Sp = rats fed on commercial diet supplemented with 5% *Spirulina*; C+CCl₄ = rats fed on commercial diet, killed at 48 h after CCl₄ administration; Sp+CCl₄ = rats fed on commercial diet supplemented with 5% *S. platensis*, killed at 48 h after CCl₄ administration. Values are mean ± SD of n=6 for each group. Significantly different both in GSH values, and in TBARs levels: C+CCl₄ vs. Sp+CCl₄ p<0.05 by one-way ANOVA, and Bonferroni's post-hoc test.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

This work was supported in part by a grant from PAPIIT-DGAPA UNAM, IN-205410. We

also thank García-Guerrero Aldo E, and Gaytán-Enriquez Meztlli for their technician collaboration.

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Toctli – Revista Internacional de Ciencia y Tecnología Biomédica
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Cd. Juárez, Chih., México 2011