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Evaluation of the Ameliorative Effects of Spirulina in Propylthiouracil Induced Hyperlipidaemia, Liver and Kidney Toxicity in Rats

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Propylthiouracil (PTU) is a drug widely used in the management of hyperthyroidism. The drug was observed to cause hepatitis and fulminant liver failure.Spirulinais documented to exhibit several therapeutic effectsincluding hepatoprotective, nephroprotective, and antioxidant activities.
Objective: This study aimed to assess the nutritional value of Spirulina,and to examine its ameliorative effects against PTU-induced hypothyroidism associated with hyperlipidemia, liver, and kidney toxicity in rats**.**
Materials and Methods: This experiment was carried out on 50 rats (5 groups, n = 10). Hypothyroidism was induced in 40 rats*via* injecting 10 mg/kg/day PTUfor 6 weeks.
Results: The results of this study showed that Spirulina contains 57.30 % of its dry weight proteins while it contains only 8.2% of its dry weight fats. It contains several minerals and vitamins (E and β-carotene).Spirulina increases the final body weight, food intake, and body weight gain % values compared to PTU rats. The Alga increased FT3 and FT4 levels, while decrease TSH level compared to PTU rats. Spirulina significantly decreased serum liver enzymes (ALT, AST, and ALP)

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and serum kidney function markers (creatinine and urea) compared to PTU rats. Besides, it reduced serum lipid profile markers (TC, TG, and LDL-C) and increased HDL-C. The Alga reduced the lipid peroxidation product and increased glutathione peroxidase concentrations.
Conclusion: The results of this study confirmed the protective role of Spirulina versus PTU associated hypothyroidism, hyperlipidemia, hepatic, and nephrotoxicity. The antioxidant impact of Spirulina may elucidate its defensive effect against various PTU toxicities.

Keywords: Propylthiouracil; hypothyroidism; hepatotoxicity; nephrotoxicity; antioxidant.

1. INTRODUCTION

The thyroid gland is an endocrine gland in the neck, consisting of two lobes connected by an isthmus[1]. It is responsible for secreting hormones that regulate the basal metabolic rate, function of tissues, and mitochondrial respiratory chain components, thus have the main impact on oxidative stress[2]. The disorder of thyroid functions may produce various subclinical or clinical manifestations[3].The prevalence of thyroid troubles is a common health problem worldwide and in Saudi Arabia too.It might disturb the antioxidant/oxidant equilibrium, where, hyper and hypothyroidism stimulate oxidative stress and oxidant-mediated tissue injuries[4–6].
Propylthiouracil (PTU) is a thioamide medicine which is widely applied in the treatment of hyperthyroidism and Graves' disease[7]. Mild leukopenia, arthralgia, fever, and rash are the most common side effects associated with its usage. Several studies have proven that PTU induces hepatotoxicity and hepatitis. PTU induced liver injuries have ranged from disturbing liver functions to acute liver failure[8]. The mechanism(s) behind PTU induced hepatic injury is not clear yet. However, metabolism, pharmacokinetic, mitochondrial injury, and defect in cellular defense may be involved in PTU induced hepatic injury[9–11]. In addition, PTU therapy may cause tubule interstitial nephritis andkidney failure *via* altering the immune response[12]. Besides, PTU produced hypothyroidism wasshown to be associatedwithnephrotoxicity *via* induction of lipid peroxidation[13]. In addition, elevated levels of lipids, lipoprotein, and apolipoprotein-B were proven in PTU induced hypothyroid in rabbits[14]. Thus, there is a necessary need for medicines against injuries induced by PTU.

Spirulina is a spiral blue-green microalga of thecyanobacterial class. This alga has a long history of use as food and can grow in many places around the world [15,16]. Spirulina is considered an excellent nutritional supplement with many health benefits, it is rich in protein, carotenoid, polyunsaturated fatty acids, glycolipids, polysaccharides, vitamins A, E, B, iodine, calcium, magnesium, manganese, potassium, selenium, zinc, and iron[17,18]. Besides, it is also a good candidate for phenolic acids, and C-phycocyanin, a powerful antioxidant, which gives spirulina its rich green color[19]. It is documented that Spirulina exhibit several therapeutic activities as hypoglycemic, hepatoprotective, nephroprotective, neuro-protective, antigenotoxic, antihypertensive, anticancer, anti-inflammatory, anti-microbial, and immunomodulation[20–28].

Therefore, this study is designed to examine the ameliorative effects of Spirulina against PTU induced hypothyroidism associated with hyperlipidemia, liver, and kidney toxicity in rats. Additionally, the mechanism behind Spirulina's effects regarding the oxidative stress pathway will be examined. Finally, the nutritional contents of Spirulina will be investigated.

2. MATERIALS AND METHODS

2.1 Chemicals

Diatom *Spirulina*powder (500 g) was obtained from Biotechnology Unit, National Research Centre (NRC), Egypt.Propylthiouracil (6-n-propyl-2-thiouracil) (PTU) was boughtfrom Amoun Pharmaceutical Company, El-Obour City, Egypt. The kits were boughtfrom Gama Trade Company for Chemicals,Egypt.

2.2 Analysis of Spirulinapowder Macro and Micronutrients Contents

Themacro and micronutrient contents of *Spirulina*were assessedfollowing the assayreported in the analytical chemists[29].

2.3 Animals

Fifty albino Sprague Dawley rats, their body weightsranged from190 to 210 gwere utilized in

this work.Rats were allowed to acclimatize for 7 days before the start of the experiment under standard lab conditions according to Canadian ethics in the animal house of Regional Center for Food and Feed, Agricultural Research Center, Giza, Egypt. They were fed on a standard diet which was formulated according to[30].

2.4 Induction of Hypothyroidism in Rats

The method of [31]was adopted to induce hypothyroidism*via* injectingPTU in 40 ratswith some modifications[32].Briefly, ratsintraperitoneal (i.p.) injected with PTU (10 mg/kg/day) for 6 weeks. After 2 weeks the blood samples were obtained from the retro-orbital plexus for serum separation,which was analyzed to compare the values of serumthyroid hormones (free triiodothyronine (FT3), free thyroxine (FT4) and thyroid-stimulating hormone (TSH)) to the control rat'svalues. Hypothyroidism is defined as significant reduction in FT3 and FT4 together witha markedelevationin TSH compared with the control values[33].

2.5 Experimental Design

This experiment includes 5 groups (n =10).Group 1: control, fed on the standard diet and i.p. injected with saline for 6 weeks. Group 2: PTU, the hypothyroidism rats were fed on the standarddiet for 6 weeks. Group 3: PTU + Spirulina 1%, the hypothyroidism rats were fed on the standarddiet for 2 weeks and then they were switched to feed on a diet containing 1% Spirulina for 4 weeks[34].Group 4: PTU + Spirulina 2%, the hypothyroidism rats were fed on the standarddiet for 2 weeks and then they were switched to feed on a diet containing 2% Spirulina for 4 weeks[34].Group 5: PTU + Spirulina 3%, the hypothyroidism rats werefed on the standard diet for 2 weeks and then they were switched to feed on a diet containing 3% Spirulinafor 4 weeks[34].The nutritional content of the diet was adjusted after adding Spirulina to match the content of the basic diet.After 6 weeks, the overnight fasted rats were anesthetized for gathering blood from the retro-orbital plexus for serum separation.

2.6 Determination of Some Biological Evaluation

Biological evaluation was carried out by determination of initial body weight (IBW), final body weight (FBW), and feed intake (FI) during the experimental period. Furthermore, the percentage of body weight gain (BWG%) was computed.

2.7 Determination of Serum Thyroid Hormones

The serum thyroid hormones (FT3, FT4, andTSH) were determined using enzyme-linked immunoscorbent assay (ELIZA) kits based on the manufacture steps.

2.8 Determination of Serum Antioxidant Measures

Malondialdehyde (MDA) and glutathione peroxidase (GPx) were determined using ELISA kits according to the manufacture instructions.

2.9 Determination of Serum Liver and Renal Functions

Aspartate aminotransaminase (AST), alanine aminotransaminase (ALT),alkaline phosphatase (ALP), creatinine, and urea were determined usingcolorimetric assay kits according to the manufacture instructions.

2.10 Determination of the serum Lipids Levels

Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were determined using colorimetric assay kits according to the manufacture instructions.

2.11 HistopathologicalExamination

The formalin-fixed liver tissues were dehydrated in graded alcohol, cleared in xylene, embedded in paraffin, cut into 3-5 µm thick sections, stained with hematoxylin and eosin (H & E), and examined under light.

2.12 Statistical Analysis

Results were expressed as the mean ± standard error (SE). Data were statistically analyzed for significance using ANOVAfollowed by LSDmultiple comparison test at $P \leq 0.05$ using SPSS software program, version 24.

3. RESULTS

3.1 Chemical Composition of Spirulina

The results of this study showed that Spirulina contains57.30 % of its dry weight proteins which

is considered a high protein value, whileit containsonly 8.2% of its dry weight fats.Spirulina contains several minerals mostlycalcium, potassium, and phosphorus. Moreover, it contains high amount of vitamin E (alpha-tocopherol) and vitamin A (β-carotene) (Table 1).

3.2 Effect of Spirulina on Some Biological Evaluation Determined in PTU Injected Rats

Rats treated with PTU for six weeks recorded significant decreasesin FBW, FI, and BWG% values compared with the control rats. The rats treated with different doses of Spirulinaalong with PTU revealed significant increases in FBW, FI, and BWG%values compared with the PTU treated group. Besides, significant increases in FBW, FI, and BWG%values were shown in the PTU rats treated with Spirulina 3 % compared withthe PTU rats treated with Spirulina 1%(Table 2).

3.3 Effect of Spirulina on Serum Thyroid Hormones Determined inPTU Injected Rats

Rats treated with PTU for six weeks recorded significant decreasesin the serum FT3 and FT4 levels, concurrent with a significant increase in the serum TSH level compared with the control group. On the other hand, the administration of Spirulina to rats along with PTU induced significant increases in the FT3 and FT4concentrations, witha significant reductionin the TSH concentration compared with the PTU injected rats. There were significant differencesin all thyroid hormones betweenPTUratstreatedwith Spirulina 1% and PTUratstreatedwith either Spirulina2%or 3%. Besides,there were significant differences in all thyroid hormones betweenPTU rats treated with Spirulina 2% and PTU rats treatedwith Spirulina 3% (Fig. 1).

3.4 Effect of Spirulina on Antioxidant Measures Determined in PTU Injected Rats

Rats administrated PTU for six weeks showed a significant decrease in serum GPX level besides a significant increase in serum MDA level compared to the control group. On the other hand, rats administrated Spirulina (1, 2, and 3%) along with PTU exhibited significant increases in serum GPX levels besidessignificant decreases in serum MDA levels compared with the PTU group.There was significant variation betweenPTUrats treatedwith Spirulina 1% and PTU rats treatedwith either Spirulina 2% or 3%. Besides,there was significant variation betweenPTU rats treatedwith Spirulina 2% and PTU rats treatedwith Spirulina 3 % (Fig. 2).

3.5 Effect of Spirulina on Serum Liver Functions Determined in PTU Injected Rats

Rats administrated PTU for six weeks showed significant increases in the serum liver enzymes levels (ALT,AST,and ALP) compared to the control group. On the other hand, PTU rats administrated Spirulina(1, 2, and 3%) exhibited significant decreases in the serum ALT,AST, and ALP levels compared to the PTU group.A significant variation was found between the PTU group consumed Spirulina 3% and the PTU group consumed either Spirulina 1% or 2% (Fig. 3).

3.6 Effect of Spirulina on Serum Kidney Functions Determined in PTU Injected Rats

Rats administrated PTU for six weeks showed significant increases in the serum creatinine and urea levels compared to the control group. On the other hand, PTU rats administrated Spirulina (1, 2, and 3%) exhibited significant decreases in the serum creatinine and urea levels compared to the PTU group. A significant variation was found between the PTU group consumed Spirulina 3% and the PTU group consumed Spirulina 1%(Fig. 4).

3.7 Effect of Spirulina on Serum Lipids Determined in PTU Injected Rats

Rats administrated PTU for six weeks showed significant increases in serum lipids levels (TC, TG, HDL-C, and LDL-C) compared to the control rats. On the other hand, PTU rats administrated Spirulina (1, 2, and 3%) exhibited significant decreases in the serum TC, TG, and LDL-C levels compared to the PTU group.Moreover, PTU rats administrated Spirulina (1, 2, and 3%) exhibited significant increase in the serum HDL-C level compared to the PTU group. A significant variation was found between the PTU group consumed Spirulina 3% and the PTU group consumed either Spirulina 1% (Table 3).

3.8 Effect of Spirulina on Liver Histopathology after PTU Injection

The control liver section showedhealthy hepatic lobuletissue(Fig. 5a). The PTU treated ratsshowed fibrosis in the portal triad and coagulative necrosis of hepatocytes (Fig. 5b). The PTU ratstreated with Spirulina 1% showing slight dilatation of hepatic sinusoids with few leucocytes(Fig. 5c). The PTU ratstreated withSpirulina 2% showing few vacuoles in the cytoplasm of hepatocytes (Fig. 5d). The PTU ratstreated withSpirulina 3% showing normal histological structure (Fig. 5e).

4. DISCUSSION

Spirulina is a bluish-greenalga rich in many active biological substances that have many medicinal uses.This study pursued to evaluate the nutritional contents of Spirulina besides evaluating the protective impacts of the alga on the function of thyroid, liver, and kidney during PTU inducedhypothyroidism.The findings of the instant study showed that Spirulina contains high protein percent; it is about 57.30 % of its dry weight this is imperative due to the good plant sources of protein contain only less than 50 % of their dry weight protein.Moreover, it contains high amount of vitamin E and β-carotene. Similar to this study [35]reported that Spirulina is a rich source of protein as it contains 62.84% of its weight protein mostly 38.46% essential amino acids. Besides, Spirulina is a perfect source of beta-carotene and vitamin E[36,37].The results of this study found that the injection of rats with PTU reduced the FBW, FI, and BWG% while treatment with Spirulina reversed all these vital changes. Like our findings, previous results have documented the decreased bodyweight that associated with either PTU or methimazole injection [38,39].The unexpected decrease in body weight that associated the hypothyroidism may be due to the effect of the high PTU dose used and the long duration of the experiment.

The results of the present study showed a decrease in the level of thyroid hormones, antioxidant levels (GPX), and an increase in the product of oxidative stress (MDA) in rats treated with PTU. This study also showed that PTUdisturbed thekidney function (increased creatinine and urea).Recent studies agree with the results of this study, where PTU caused a significant decrease in thyroid hormones in adult and newborn rats. The studies also reported a decrease in kidney function, which was accompanied by a rise in oxidative products in experimental rats[32,40].Treatment with Spirulina resulted in a marked improvement in thyroid function, kidney function, and GPX antioxidant in this study.In a recent study, its results violated the results of this study, as the use of Spirulina in the PTU treated rats resulted in a noticeable increase in T3 and T4 and an unnoticeable decrease in TSH. While the researchers reported a slight improvement in the tissue of the thyroid gland.The improvement in thyroid tissue observed may be due to the Spirulina content of iodine, which improves the composition and function of the thyroid gland[38,41].In a recent study in agreement with our results, the researchers reported the preventive effect of feedingSpirulina and its active ingredient C-phycocyanin on kidney function in the chronic renal toxicity model in rats[42]. Behind this lies the anti-inflammatory, antioxidant, and the lowering peripheral vascular resistance induced by Spirulina[43,44].

Early studies have noted the emergence of isolated and rare cases of hepatitis and fulminant liver failure associated with treatment with PTU [45,46].The global incidence of hepatotoxicity associated with PTUtreatment is about 0.1% in the adult patients besides 10% of them may progress toacute liver failure[47].

The results of this study revealed that treatment of rats with PTU significantly increased liver enzymes leakage into the serum which indicated hepatocytes inflammation and necrosis. These biochemical findings were also confirmed by the liver histopathological findings includingfibrosis in the portal triad and coagulative necrosis of hepatocytes.Similar results were previously reported by[48] who showed that PTU induced liver damage was associated with several histopathological alterations like portal region inflammation, hepatitis, and hepatocytes necrosis. The research also reported that the histological changes in the liver after administeringPTU are similar to autoimmune hepatitis type I. The cause of hepatitis associated with PTU is due to either hypersensitivity or idiosyncratic reactions[49–51].

In the current study, it was found that consuming Spirulina in ascending doses caused a significant decrease in the levels of liver enzymes (ALT, AST, and ALP) compared to rats in the PTU group. Also, the consumption of Spirulina has improved liver tissue upon histopathological examination. Besides, the results showed a

reduced effect of different blood lipids (TC, TG, and LDL-C) in the rats treated with Spirulina relative to the PTU group.In agreement with the results of the current study, the researchers advised that consuming Spirulina supplement daily for a period of 6 months had reduced elevated liver enzymes associated with non- alcoholic fatty hepatitis. Also, the effect of Spirulina was associatedwith a decreasedconcentration of blood fat as well[52,53].Moreover, a recently published manuscript documented that Spirulina improved virus C hepatitis and reduced liver enzymes (ALT and AST) in β-thalassemia major diseased children by decreasing serum ferritin and ameliorated immunity[54].The hepatoprotective mechanism of Spirulina against liver damage induced in rats and humans is due to the richness of this Algae with antioxidants and anti-inflammatories including vitamin E, C-phycocyanin, and β-carotene, as well as its ability to get rid of excess liver lipids[55–57]. The lipid-lowering mechanism for this Alga lies in its ability to reduce the level of triglyceridesas studies have proven to contain a high level of protein and very little fat [58–60].

Table 1. Chemical composition, macro-micro-nutrients contents, of Spirulina

Components	Mean ± SE
Moisture (%)	7.10 ± 0.87
Protein (%)	57.30 ±1.09
Fats (%)	8.20 ± 0.69
Ash (%)	9.60 ± 0.92
Fiber (%)	4.30 ± 0.98
Carbohydrate (%)	13.50 ± 1.44
Minerals(mg/100 g)	
Calcium	289.50 ± 3.18
Phosphorus	118.27 ± 3.84
Potassium	184.2 ± 0.69
Iron	11.90 ± 1.15
Zinc	2.80 ± 0.58
Manganese	9.10 ± 1.15
Copper	5.80 ± 1.04
Sodium	220.30 ± 11.55
Vitamins (mg/100 g)	
Vitamin E (Alpha-tocopherol)	56.90 ± 5.77
Vitamin A (β-Carotene)	68.70 ± 5.78
Vitamin B1 (Thiamine)	3.80± 0.58
Vitamin B2 (Riboflavin)	4.10 ± 0.58

Values were presented as the mean of three replicates ± SE

Table 2. Effect of Spirulina on some biological parameters determined in PTU injected rats

Experimental groups	IBW (g)	FBW (g)	FI (g/day/rat)	BWG%
Control	200.7 ± 2.22	263.1 ± 3.77	20.9 ± 0.85	31.09 ± 1.29
PTU	200.6 ± 2.24	231.2 ± 3.74 [a]	12.1 ± 1.10 [a]	15.25 ± 0.71 [a]
PTU+ Spirulina 1%	201.5 ± 2.10	241.6 ± 3.15[b]	15.1 ± 1.03 [b]	19.91 ± 2.33 [b]
PTU+ Spirulina 2%	200.5 ± 2.02	246.9 ± 4.06[b]	17.5 ± 1.04[b]	23.14 ± 1.79 [b]
PTU+ Spirulina 3%	200.8 ± 2.05	253.2 ± 3.20[b, c]	19.0 ± 1.03 [b, c]	26.10 ± 0.76 [b, c]

Values were offered as mean ± SE (n=10). Results were significantly varied (P < 0.05)from [a]: control negative. [b]:PTU group. [c]: PTU + Spirulina1% group.

IBW: Initial body weight; FBW: Final body weight; FI: Feed intake; BWG%: Body weight gain percent; FER: Feed efficiency ratio

Table 3. Effect of Spirulina on serum lipids determined in PTU injected rats

Experimental groups	TC (mg/dl)	TG (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)
Control	98.70 ± 4.90	92.30 ± 2.04	37.10 ± 1.62	42.30 ± 0.97
PTU	137.80 ± 3.15 [a]	164.10 ± 2.83 [a]	26.50 ± 2.10 [a]	76.80 ± 3.01 [a]
PTU+ Spirulina 1%	125.20 ± 3.65 [b]	125.70 ± 4.23 [b]	32.20 ± 1.72 [b]	54.20 ± 3.37 [b]
PTU+ Spirulina 2%	118.70 ± 5.87 [b]	114.70 ± 5.39[b]	35.60 ± 1.24 [b]	48.10 ± 1.92 [b]
PTU+ Spirulina 3%	106.60 ± 3.60[b,c]	107.30 ± 3.98[b,c]	38.70 ± 2.21[b,c]	45.80 ± 1.44[b,c]

Values were offeredas mean ± SE (n=10). Results were significantly varied (P < 0.05)from [a]: control negative. [b]: PTU group. [c]: PTU + Spirulina 1% group.
TC: Total cholesterol; TG: Triglycerides; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol

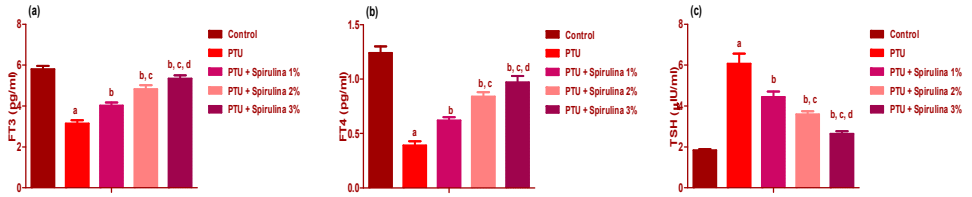

Fig. 1. Effect of Spirulina on serum thyroid hormones determined in PTU injected rats
Values were offeredas mean ± SE (n=10). Results were significantly varied (P< 0.05) from [a]: control negative. [b]: PTU group. [c]: PTU + Spirulina 1% group. [d]: PTU + Spirulina 2% group.
FT3: Free triiodothyronine; FT4: Free thyroxine; TSH: Thyroid-stimulating hormone

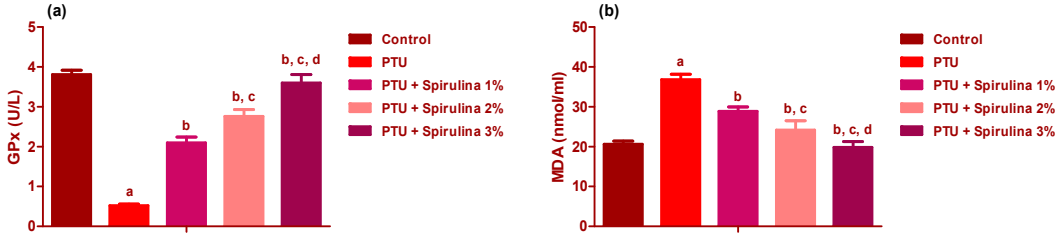

Fig. 2. Effect of Spirulina on antioxidant measures determined in PTU injected rats
Values were offeredas mean ± SE (n=10). Results were significantly varied (P < 0.05)from [a]: control negative. [b]: PTU group. [c]: PTU + Spirulina 1% group. [d]: PTU + Spirulina 2% group.
GPx: Glutathione peroxidase; MDA:Malondialdehyde

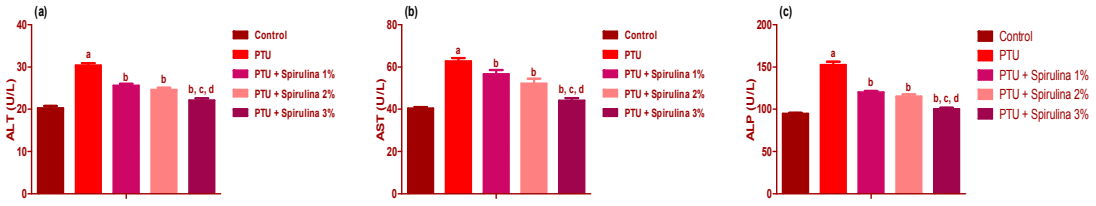

Fig. 3. Effect of Spirulina on serum liver functions determined in PTU injected rats
Values were presented as mean ± SE (n=10). Results were significantly varied (P < 0.05)from [a]: control negative. [b]: PTU group. [c]: PTU + Spirulina 1% group. [d]: PTU + Spirulina 2% group.
ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase

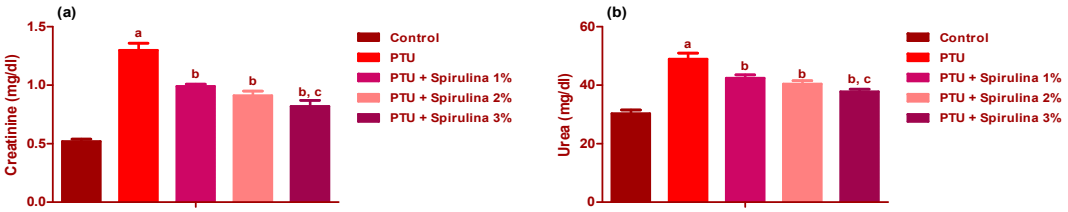

Fig. 4. Effect of Spirulina on serum kidneyfunctions determined in PTU injected rats

Values were presented as mean ± SE (n=10). Results were significantly varied (P < 0.05)from [a]: control negative.[b]: PTU group. [c]: PTU + Spirulina 1% group

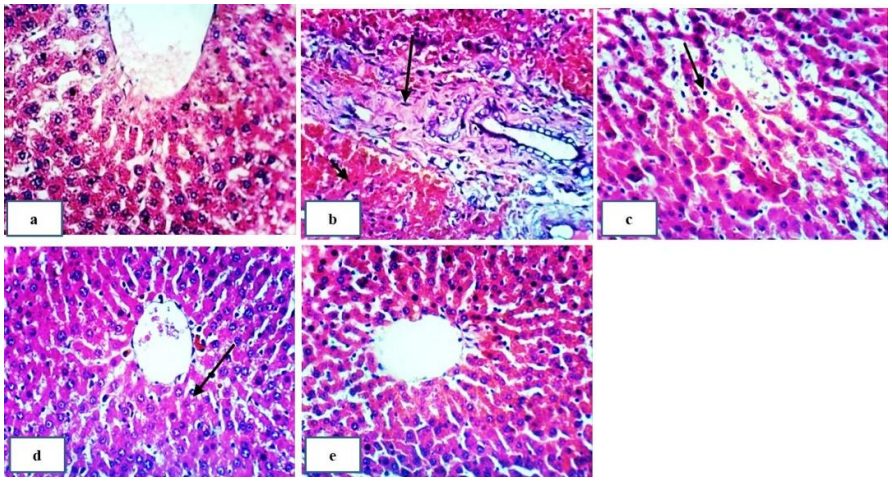

Fig. 5. Effect of Spirulina on liver histopathological alteration (H&E x 400)

Control (a): showing normal structure of hepatic lobule. PTU (b): showing fibrosis in the portal triad (small arrow) and coagulative necrosis of hepatocytes (large arrow). PTU+ Spirulina 1% (c): showing slight dilatation of hepatic sinusoids with few leucocytes (arrow).PTU+ Spirulina 2% (d): showing few vacuoles in the cytoplasm of hepatocytes (arrow). PTU+ Spirulina 3% (e): showing normal histological structure

5. CONCLUSION

The results of this work presented good evidence about the protective action of Spirulina against PTU induced hypothyroidism, hyperlipidemia, hepatic and nephrotoxicity. The antioxidant effect of Spirulina may explain its protective action against the different PTU toxicities.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The research carry out according to Canadian ethics in the animal house of Regional Center for Food and Feed, Agricultural Research Center, Giza, Egypt.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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