Journal of Fundamental and Applied Sciences

ISSN 1112-9867

Available online at http://www.jfas.info

Research Article

A LOW-DOSE PROTECTIVE EFFECT OF PHYCOCYANIN ON THE TOXICITY OF DELTAMETHRIN TO VITAL ORGANS IN RATS: IN VIVO STUDY

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Received: 20 October 2019 / Accepted: 19 December 2019 / Published online: 01 January 2020

ABSTRACT

The study highlights the histopathological alterations of the liver, kidney and heart of female rats exposed to a low dose of deltamethrin (DLM), the potential hepatoprotective, nephroprotective and cardioprotective effects of phycocyanin.

Twenty-four (24) female Albino Wistar rats divided into four groups recognised as follows: Control rats received a standard diet (C). Group (PC) treated with a standard diet enriched with 3.6 ± 0.1 mg of phycocyanin per kg of granules. Group (DLM) treated with a standard diet combined with DLM in water at a concentration of 1.28 mg per kg body weight per day. The remaining group (DLM / PC) was processed by the combination of the DLM and PC scheme.

The toxicity of DLM was revealed by transaminase analysis and histological observation.

The association (DLM + PC) revealed a protective effect of phycocyanin as illustrated by the reduction of the concentration of serum AST and the important decrease of lesions in the tissues studied. Therefore, it shows that PC has a protective action against the toxic effects of DLM.

Keywords: Pyrethroid; phycocyanin; hepatoprotective; nephroprotective; cardioprotective.

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doi: http://dx.doi.org/10.4314/jfas.v12i1.11

1. INTRODUCTION

Cyanobacteria are unique prokaryotes capable of photosynthesis. In these organisms, phycobilisomes (PBS) act as an antenna of the pigmented photosynthetic apparatus. The latter composed of several phycobiliproteins (PBP) including: phycoerythrin (PE), phycocyanin (PC), allophycocyanin (APC) and phycoerythrocyanin (PEC) [1].

Phycocyanin is one of the main pigments of spirulina alga (cyanobacteria) [2, 3]. PC is composed of a protein and a non-protein component known as phycocyanobilin (PCB), the latter is structurally similar to bilirubin and biliverdin, of open-chain tetrapyrrole form; the origin of the intense blue color characteristic of phycocyanin [2].

A potent antioxidant, phycocyanin is capable of trapping several radicals such as: hydroxyl radicals, peroxyl radicals, singlet oxygen, superoxide anions and hydrogen peroxide [2-5].

It stimulates immunity and prevents oxidative damages, which may partly explain its anti-tumor effects [6,7], anti-inflammatory [8,9], hepatoprotective, cardio-protective, neuroprotective [2] and nephroprotective [10]. In regards to nutraceutical, its use has increased rapidly in recent years in the field of biotechnology and pharmaceuticals [1,11], widely used in the food and cosmetics industry as natural blue dye [7], and due to its fluorescence properties, pure PC is used as a marker in immunology, microscopy and cytometry [12].

The intensive use of pesticides is associated with environmental and human impacts with high levels of liver failure, kidney failure, infertility, cancer, immunosuppression and neurological diseases [13]. Among the pesticides are the pyrethroid insecticides, which are the synthetic derivatives of natural pyrethrins obtained from pyrethrum flowers [14], which later became the main substitutes for organophosphorus compounds [15]. Deltamethrin (DLM) is a synthetic pyrethroid type II broad-spectrum [13], chemical formula [α-cyano-3-phenoxybenzyl- (1R, S) -Cis, trans-3- (2,2- dibromovinyl) -2,2 dimethylcyclopropanecarboxylate] [16], widely used in the agricultural field to protect vegetables, fruits, also used against pests such as : mites, ants, beetles and weevils [13,17].

In veterinary practice, DLM is used as an ectoparasiticide against mites, flies, ticks and fleas to control vector-borne diseases [18]. DLM has become an insecticide of choice in most countries owing to its high potency against a large number of pests, its rapid degradation and low toxicity

to humans as well as non-target animals [16]. Birds, animals and humans living in the same ecosystem are directly or indirectly exposed to the risk of DLM [19].

A number of studies concerning the side effects of this insecticide have been reported, including hepatotoxicity and neurotoxicity [13], nephrotoxicity [20], cardiovascular abnormalities [21], immunosuppression [22] and side effects on reproduction [14].

Recently, several publications have been the subject of in vivo studies on the protective role of Spirulina with regards to the toxic effects caused by DLM [13,15,23].

It is assumed that phycocyanin and the powerful antioxidant of spirulina could be the origin of the protective effects of spirulina.

The main objective of this study is to determine the effects of very low doses of phycocyanin on metabolic abnormalities as well as its antagonistic role on the hepatotoxicity, nephrotoxicity and cardiotoxicity induced by subacute DLM treatment in albino rats.

2. RESULTS AND DISCUSSION

Determination of the purity of C-phycocyanin:

After extraction and purification of the PC from spirulina, the degree of purity calculated on the basis of the ratio between the two absorbances at 620 and 280 nm is 0.15 ± 0.04.

Since A 620 / A 280 (0.15) ≤ 0.7, C-PC is considered food grade [6].

Estimation of phycobiliproteins:

After evaluating the main antioxidant components of phycobiliproteins extracted from spirulina [28], the values obtained for C-PC, APC and PE were 0.06 ± 0.02, 0.03 ± 0.00 and 0, 01 ± 0.00 mg / mL respectively.

Restorative effect of phycocyanin on the effects of DLM on serum AST:

The data on transaminase levels in the serum of experimental rats are presented in Tables 1 mentioned below:

Table 1. Effect of DLM and / or PC on serum transaminase levels in rats

Paramètres	**Croups**			
	Control **n=6**	**PC** **n=6**	**DLM** **n=6**	**DLM/PC** **n=6**
AST (UI/L)	140.26±20.17	136.83±16.51	188.66 ±49.78***	154.5±17.79***
ALT (UI/L)	47.13±8.06	62±7.36	53.44±11.89	50.28±13.23

The values are represented on average ± standard deviation. Values in the same row with different superscript letters are significantly different (P < 0.05).

Administration of the 0.04% DLM caused a significant increase (P≤0.01) in serum AST concentration (DLM group) of 188.66 (IU / L) in comparison with the control group 140.26 (IU / L). The addition of PC to the diet of the DLM-treated rats (DLM / PC group) significantly lowered the serum AST level 154.5 (IU / L), compared with the DLM group after four weeks of treatment (Figure 1).

In contrast, ingestion of DLM did not have significant effects on the concentration of ALT transaminase.

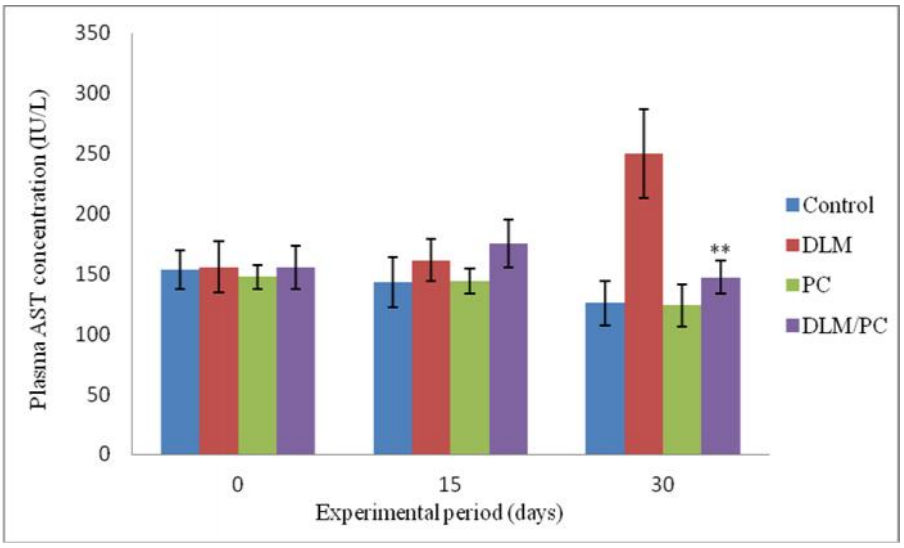

Fig.1. Comparison of serum AST (IU / L) concentrations in female rat groups treated with PC, DLM and DLM / PC and the control group. The values are represented on average ± standard deviation. Values in the same row with different superscript letters are significantly different (P<0.05)

Histology:

Subacute intoxication caused by deltamethrin and improvement's effects of phycocyanin were evaluated from histological sections of the liver, kidneys and heart. The liver of DLM-poisoned rats exhibits perivascular hepatocyte degeneration with predominantly centrolobular localization (fig.2 (d)), as well as periportal inflammation of the lymphoplasmacytic type (fig.2 (b)).

Moreover, it is observed that the presence of mixed intraparenchymal inflammatory foci composed of lymphocytes, histiocytes and some neutrophils (fig.2 (c)), as well as the presence of inflammatory cells in the sinusoids (mainly lymphocytes and neutrophils) (fig.2 (b.c)).

Ingesting phycocyanin remarkably decreases the intensity and distribution of hepatocyte degeneration, as well as the intensity and distribution of inflammation (fig.2 (e)).

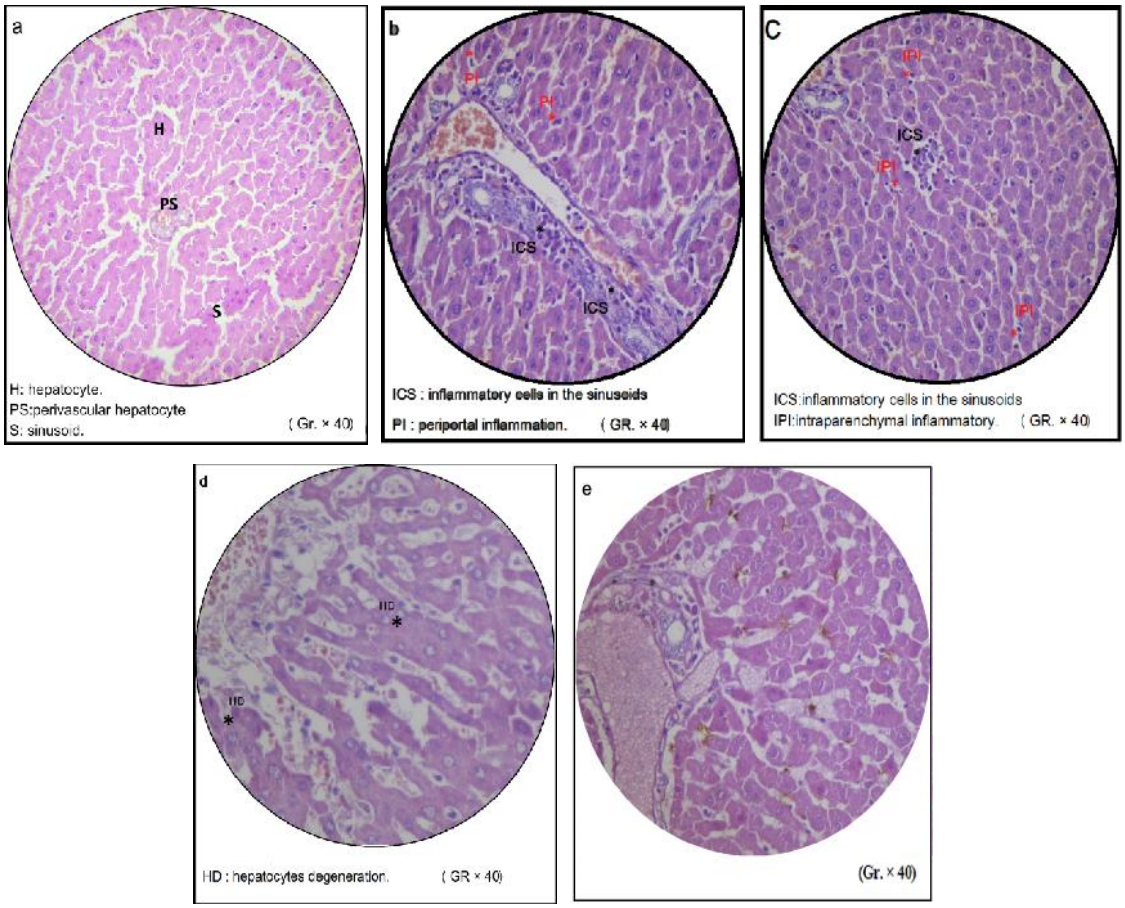

Fig.2. Effects of phycocyanin on DLM-induced hepatotoxicity

The DLM kidney control showed degeneration of tubular epithelial cells (proximal and distal convoluted tubules) (fig.3 (c.d.e)), mesangial cell hyperplasia (fig.3 (b)) and multifocal glomerular retraction (fig.3 (c.e)).

It is marked by a decrease in the frequency and intensity of glomerular retraction, hence, the renal tissue of the DLM/PC group (fig.3 (f)) has a similar appearance to that aspect of the negative control (fig.3 (a)).

More and above, it highlights the decrease in the intensity of mesangial cell hyperplasia and also a slight decline in the intensity of tubular epithelial degeneration compared to the DLM control, this is illustrated below through (Figure 3).

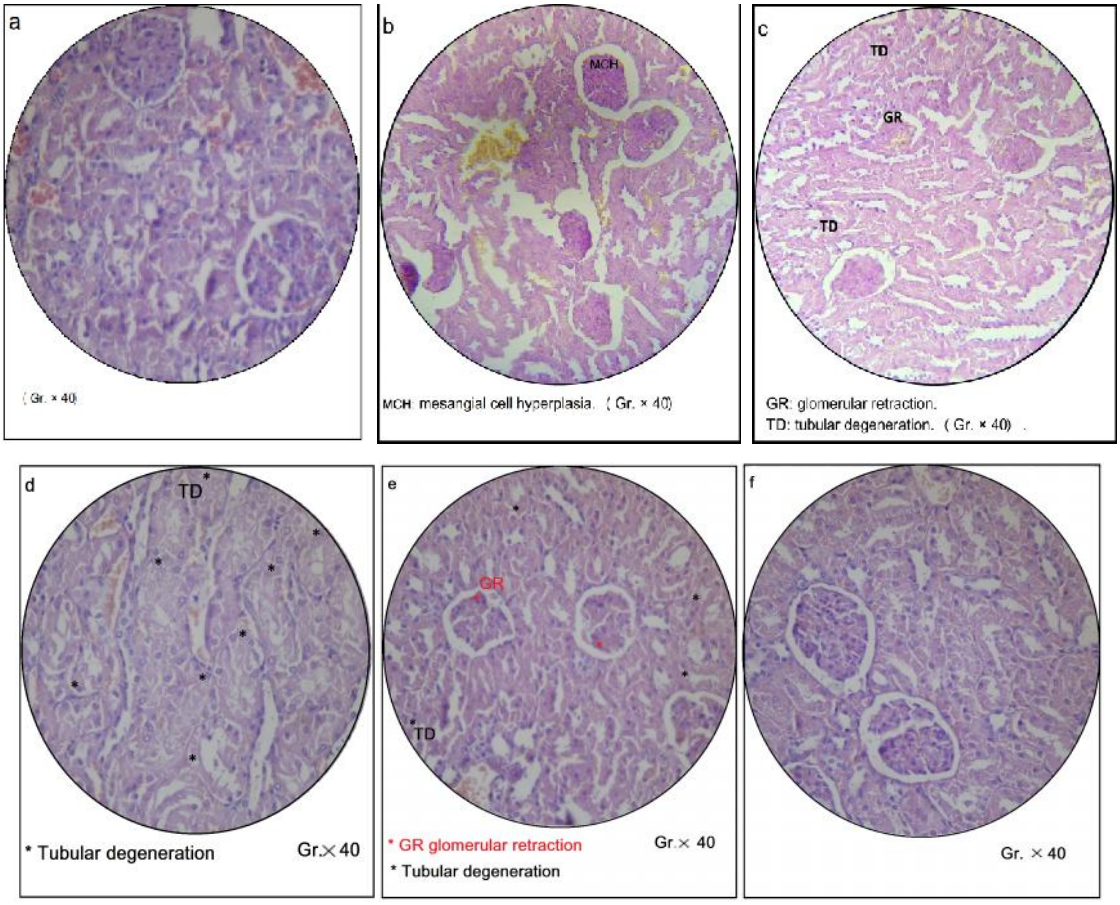

Fig.3. Effects of phycocyanin on nephrotoxicity caused by DLM

The heart tissue of the DLM control is characterized by the presence of interstitial microhemorrhages and the degeneration of the cardiac muscle fibers (fig.4 (b.c.d)). Compared with the DLM control, the cardiac tissue of DLM/PC group shows the persistence of interstitial

microhemorrhages with a decrease in intensity and distribution (fig.4 (e)), as well as the intensity and distribution of cardiac muscle degeneration, shown below in (Figure 4).

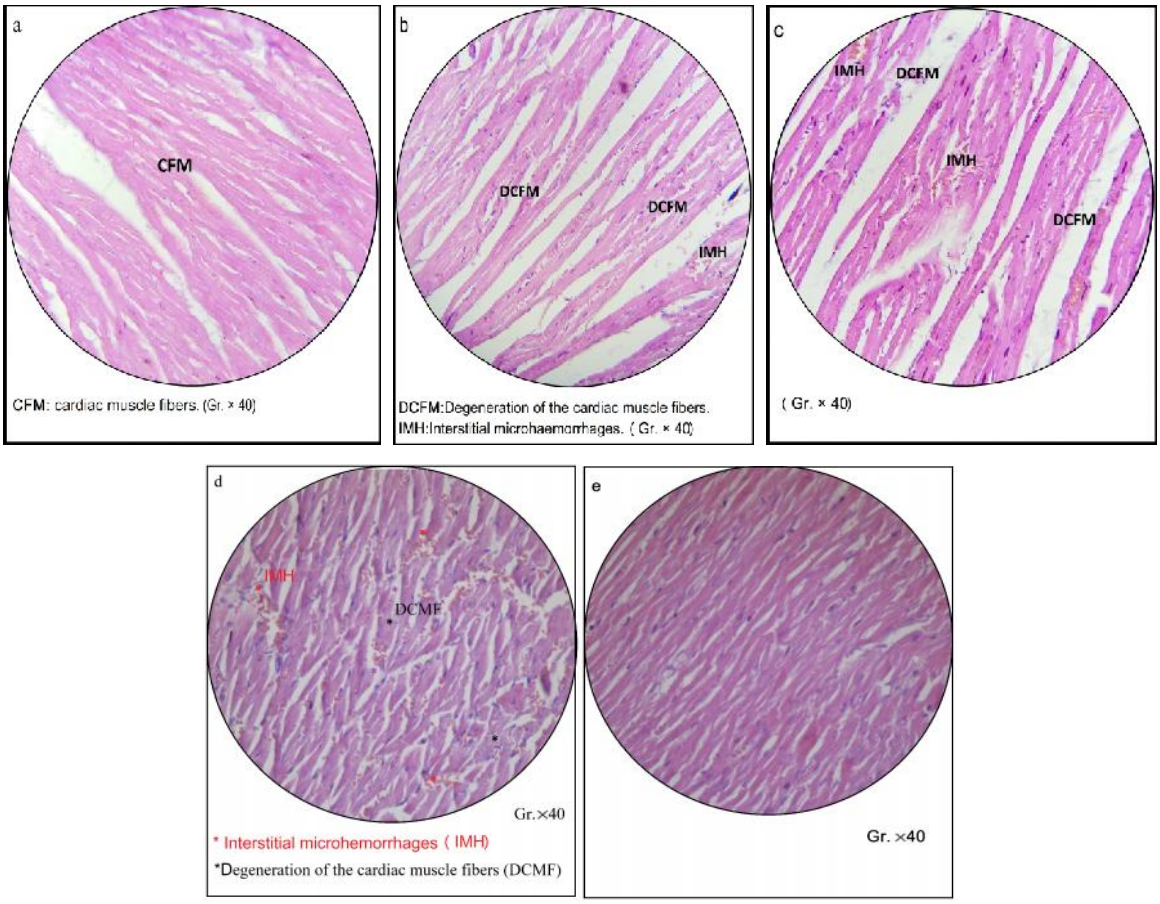

Fig.4. Effects of phycocyanin on cardiotoxicity caused by DLM

Discussion:

The reactive oxygen species (ROS) are continually generated within the animal body due to its exposure to many drugs and xenobiotics from our environment and / or through many endogenous metabolic processes involving enzyme redox and through the mechanism of bioenergetic electron transport [29]. Under normal conditions, there is a balance between the generated ROS and endogenous antioxidants that neutralize them [29]. The harmful effects caused by ROS are resulted from their overproduction that leads to both oxidative stress and chronic inflammation, which induces induces an alteration of cellular functions in return. Therefore, it contributes to the different pathological states [29-31].

DLM has become a useful insecticide in several countries due to its rapid metabolism and low toxicity to humans and non-target animals. On top of this, DLM has a high efficacy on a large bunch of pets [32]. The use of DLM has grown worldwide, in particular, in areas impacted by vector-borne diseases [33].

During pyrethroid metabolism, reactive oxygen species (ROS) are generated, and they then result in oxidative stress in intoxicated animals [14]. It is accepted that DLM has widespread toxic manifestations. DLM induces oxidative damage by producing reactive oxygen species and also by declining the biological activities of renal, hepatic and cerebral enzymatic antioxidants, such as: SOD, CAT and GPx [32,34]. It can cause allergies, hepatotoxicity, nephrotoxicity, genotoxicity and mutagenicity through immunosuppression and infertility [32]. Although several reports on the toxicity of DLM have been published, few studies have been conducted on the use of natural products for the prevention of such toxicity. In the present study, the hepatorenal and cardiac lesions caused by DLM can be attributed to the oxidative stress resulting from the overproduction of free radicals. Plasma determination of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in DLM-treated rats showed a significant increase ($P \leq 0.01$) in AST after 30 days and demonstrated no significant soar in ALT during this period.

These results represent damages to heart, liver and kidney dysfunction in DLM-treated rats. These results are consistent with other works, which suggest that DLM induces oxidative stress [15,16,35,36].

In the present study, PC supplementation at a concentration of 0.36% reduced serum AST levels, and this may be due to its high antioxidant activity and its ability to trap free radicals [7]. Due to the fact that the liver is the main organ of various metabolic pathways whereas the kidney is the fundamental organ of excretion of drugs and xenobiotics. This will lead to the toxic effects of chemicals appear mainly in liver and kidney tissues [37].

The histological study confirms the antioxidant properties of the phycocyanin extract. Exposure to deltamethrin caused degeneration of hepatocytes, periportal inflammation, intraparenchymal inflammatory foci, tubular epithelial degeneration, mesangial cell hyperplasia and renal

multifocal glomerular group, which has been exposed to the DLM in order to testify about the hepatorenal involvement.

Histopathological findings confirmed the remarkable protection of PC against hepatitis and DLM-induced nephrotoxicity.

It has been reported that pyrethroids can cause severe toxic cardiovascular events [21].

Throughout this study, it can be observed that the presence of interstitial microhemorrhages and degeneration of cardiac muscle fibers are indicating acute cardiac damages in the exposed group DLM. Histopathological findings also emphasized that the remarkable protection of PC against cardiotoxicity induced by DLM. The hepatorenal and cardiac lesions described in this study are caused by DLM that can be attributed to the increased status of oxidative stress [15]. The hepatoprotective, nephroprotective and cardioprotective effects of phycocyanin could be either direct by decreasing the level of intracellular ROS or by trapping free radicals, including peroxyls, and hydroxyl radicals [15]. Moreover, the dependence on its ability to selectively inhibit COX -2 [38], which is indirect by its ability to increase the level of reduced Glutathione (GSH) by improving mitochondrial function and decreasing the activity of intracellular cathepsin B [35]. Therefore, PC could be used as a preventive and therapeutic agent against oxidative diseases of the kidney, liver and heart.

3. EXPERIMENTAL

Chemicals:

Deltamethrin (DECIS 25 EC25 g / L) was purchased as a commercial product formulated by BAYER (Spain), a supplier of active ingredient (Germany). Spirulina (spirulhiri), produced in the south of Algeria (Tamanrasset region), was bought in the form of dried sticks from Eurl HIRI Abdelkader.

Extraction and purification of phycocyanin

It took place at the laboratory of the National Center for Research in Biotechnology (CRBT) of Constantine. The phycocyanin was extracted from Spirulina sample (previously dried as sticks) by maceration and then subjected to freeze / thaw cycles as described below:

- **Extraction:**

The dry biomass was crushed and homogenized using a mixer. For 250 gr of spirulina powder, it was added 2.5 L of phosphate buffer solution (0.05M, pH 7) and then added with sodium azide (1mM this suspension was subjected to two cycles of freezing / thawing for 48 hours [11] and then centrifuged at 15000 rpm at 4 ° C).

- **Purification:**

After the recovery of the supernatant containing the phycocyanin, it is fractionated by precipitation with ammonium sulphate at first 25% and then 50% saturation [24].

The precipitate from 25% saturation of sulphate of ammonium is eliminated [24].

The supernatant is brought to 50% saturation of solid ammonium sulphate. It is remaining for 4 hours at 4 ° C in the dark [24]. The suspension obtained is centrifuged at 15000 rpm at 4 ° C, a supernatant containing phycocyanin is obtained.

Determination of the purity of C-phycocyanin:

The purity of C-phycocyanin is evaluated on the basis of the ratio between the two absorbances at 620 and 280 nm corresponding to those of C-phycocyanin and proteins [25], it is calculated using the following equation [6] :

$$\text{Purity C-PC} = A620/A280$$

Depending on the purity range, C-PC is considered the food grade, reactive or analytical as detailed below [6]:

A 620 / A 280 ≤ 0,7, la C-PC is considered food grade ;

0,7≤A 620 / A 280 ≤ 3,9, la C-PC is considered of reagent quality;

A 620 / A 280 ≥ 4,0, la C-PC is considered of an analytical level.

Estimation of phycobiliproteins:

The dark blue supernatant containing phycobiliproteins was collected. Absorbances of phycobiliproteins were measured on a microplate reader (EnSpire from Perkin Elmer Multimode) at wavelengths 620.652 and 562 nm, for calculating phycocyanin (C-PC), allophycocyanin (APC) and phycoerythrin PE concentrations. The following equations (1-3) have been used [6,26]:

$$\text{C-PC (mg/mL)} = [A620 - 0{,}474(A652)]/5{,}34 \quad (1)$$

$$\text{APC (mg/mL)} = [A652 - 0{,}208(A620)]/5{,}09 \quad (2)$$

$$\text{PE (mg/mL)} = [A562 - 2{,}41(\text{C-PC}) - 0{,}849(\text{APC})]/9{,}62 \quad (3)$$

Following its extraction, the phycocyanin was lyophilized and then incorporated in the standard pellet diet at an exact rate of 3.6 ± 0.1 mg per kg of granules.

Animals, diet and experimental model:

Twenty-four (24) adult rats (Wistar strain, age: 10-12 weeks, weight: 150-170 g, sex: female) obtained from the Pasteur Institute of Algeria (Kouba Annex). The animal testing was conducted at the animal center of the Research and Development Center of the Algerian pharmaceutical industry SAIDAL (CRD SAIDAL).

The animals were housed in plastic cages with stainless steel grates (06 subjects / cage), food and water were provided ad libitum, maintained under normal temperature conditions (24 ± 2 ° C) and humidity (60 - 70%), with a 12 hour light / dark cycle. All animal testing was carried out according to the guidelines of the CRD belonging to the SAIDAL group (Pharmaceutical Industry of Algeria) for the care and experimentation on laboratory animals.

Two weeks later (acclimation period), the rats were randomly divided into four different groups; 6 animals each. During the experimental period, each group was fed with one of the diets shown in Figure 5 below:

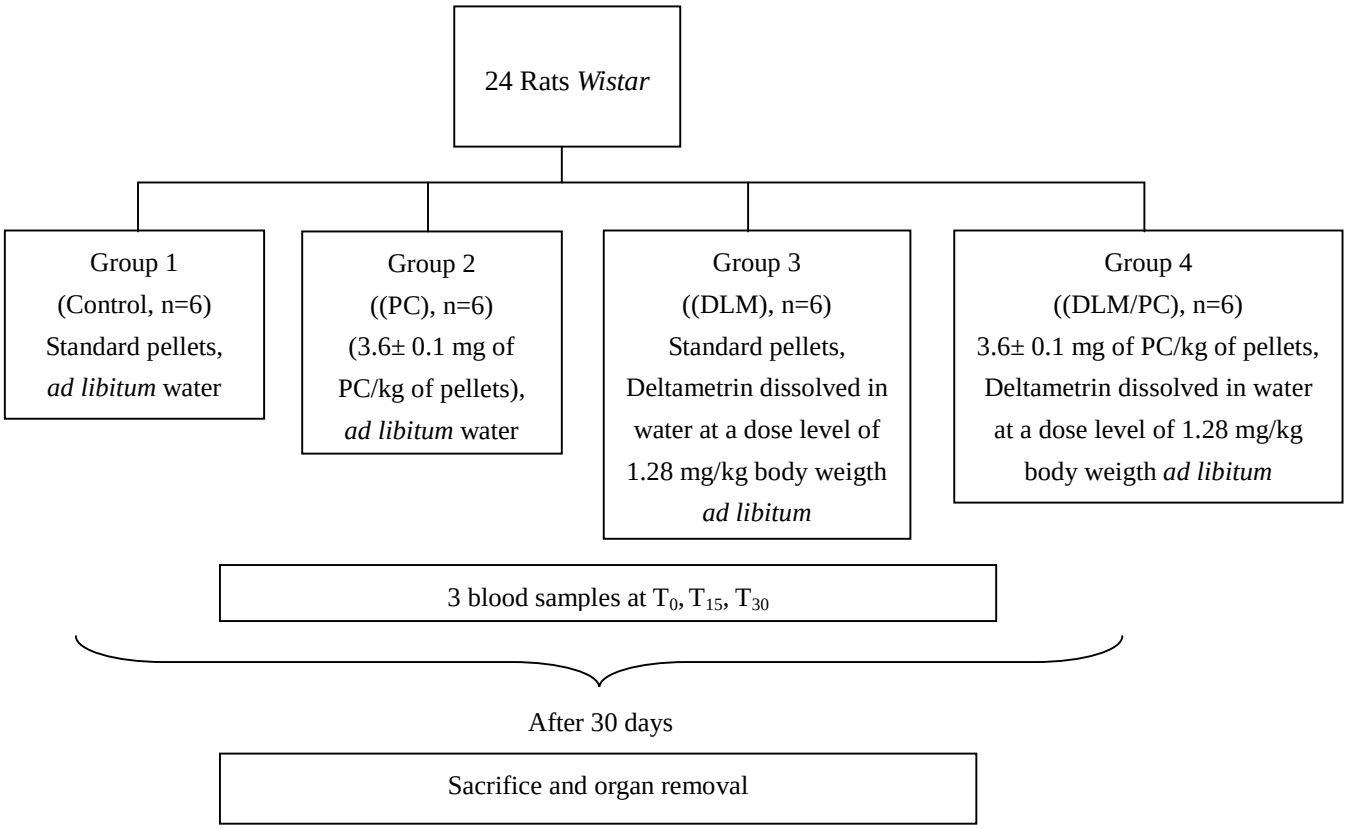

Fig.5. Diagram of the experimental protocol

Blood collection and biochemical analyzes:

Blood samples were collected from the retro-orbital plexus every 15 days following a fast of approximately 18 hours. The blood was centrifuged at 3500 rpm for 15 minutes at room temperature (25 ° C). Plasma was stored in dry tubes at -20 ° C until biochemical assays were performed.

It is monitored that the serum level of transaminases L-aspartate: 2 oxoglutarate Aminotransferase (AST) and alanine aminotransferase (ALT).

In order to have an indication of the degree of tissue involvement of the three target organs, (namely: liver, kidneys and heart), it is by using ADVIA (ADVIA 1800 Chemistry System brand SIEMENS) automated analyzer based on the photometric method.

Organs:

At the end of the experiments (30 days), animals had been fasting for nearly 18 hours and then sacrificed by cervical dislocation. The organs (liver, heart and kidney) were fixed in 10%

buffered formalin (4% v/v formaldehyde, 0.1 M phosphate buffer, pH 7.2) for histological analysis.

Tissue preparation and histological examination:

The fixed tissues were embedded in paraffin, cut into 3 µm sections and then stained with Hematoxylin / Eosin (H&E) (Zidani *et al*. 2016) and examined under a light microscope (Olympus Corporation Model Cx23ledrfs1) Gr x10, x40.

Statistics:

The results are expressed as mean ± standard deviation. The statistical analyses of the data were carried out using the Microsoft Excel Software (Microsoft Excel 2007). We used the Student Test (t-test) for comparison between means.

4. CONCLUSION

Oxidative stress plays a major role in the toxicity caused by DLM. The protective effect of C-PC against hepatotoxicity, nephrotoxicity and DLM-induced cardiotoxicity was linked with the ability of PC to trap ROS and promote antioxidant activity.

The specific data suggest that the human consumption of PC may be useful for the prevention and / or treatment of hepatorenal, as well as cardiac diseases associated with oxidative stress. An additional pre-clinical investigation must be performed.

5. ACKNOWLEDGEMENTS

The authors acknowledge those who contributed to the accomplishment of the task (“the National Center for Biotechnology Research of Constantine” and “research and development center of SAIDAL -pharmaceutical industry-”). Not to mention those of the Pasteur Institute of Algeria and the Mustapha Pasha University Hospital Center in Algiers.

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How to cite this article:
Bouzar AC, Benali Y, Bitam A. A low-dose protective effect of phycocyanin on the toxicity of deltamethrin to vital organs in rats: in vivo study. J. Fundam. Appl. Sci., 2020, *12(1), 149-166.*