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ANTI-INFLAMMATORY POTENTIAL IN EXPERIMENTAL MODELS OF PHYCOCYANIN OBTAINED FROM SPIRULINA PLATENSIS THROUGH A GREEN METHOD

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Abstract— Phycocyanin (PC) is a water-soluble biliprotein derived from Spirulina platensis, which, beyond its photosynthetic function, exhibits distinct biological activities of pharmacological significance. The present study aimed to evaluate the anti-inflammatory potential of phycocyanin extracted from Spirulina platensis using modern green extraction techniques on experimental models. Phycocyanin was isolated by ultrasonic extraction at 40 °C and 40 kHz, followed by purification and lyophilization, yielding 14.88 mg/g with a purity index of 1.60. To evaluate the anti-inflammatory properties, histamine- and carrageenan-induced rat paw edema models were used. Oral administration of phycocyanin at doses of 50, 200, and 300 mg/kg bw resulted in a statistically significant, dose-dependent inhibition of inflammatory edema. The observed activity is probably associated with modulation of TLR and NF-κB signaling pathways, reduction of proinflammatory cytokines, as well as antioxidant and anti-apoptotic mechanisms.

These results confirm that phycocyanin, extracted by an environmentally friendly method, combines high safety with marked anti-inflammatory potential. These features position it as a promising candidate for the development of nutraceuticals and pharmaceutical products targeting inflammatory disorders.

Keywords—anti-inflammatory properties, phycocyanin, Spirulina platensis, paw edema

I. INTRODUCTION

Microalgae and cyanobacteria are sources of biologically active compounds, among which the most widespread are water-soluble biliproteins collectively known as phycocyanins, exhibiting a broad spectrum of biological effects [1]. According to their spectral characteristics and origin, phycocyanins are divided into three main groups [2-4]:

C-phycocyanin (C-PC) – mainly extracted from Arthrospira platensis, showing a single absorption maximum at 620 nm;

R-phycocyanin (R-PC) – characteristic of red algae, exhibiting two absorption peaks: one around 550 nm due to phycoerythrobilin and another around 615–620 nm attributed to phycocyanobilin;

Allophycocyanin (APC) – found in both red and blue-green algae, with an absorption maximum near 650 nm.

Phycocyanin, and in particular that from Spirulina platensis, exhibits numerous pharmacological effects. There is evidence that C-phycocyanin accelerates the process of skin wound healing due to its ability to modulate various biological mechanisms [5]. Accelerated wound closure has also been reported in a mouse model treated with a topical cream containing phycocyanin from Spirulina platensis [6-7]. Refai et al. (2023) demonstrated that nanophytosomes of Spirulina platensis enhance healing of excisional wounds in rats [7]. Beyond wound healing, the multifaceted biological activities of phycocyanin make it a promising candidate for topical treatment of various dermatological conditions [5].

According to Liu et al. (2022) [8], phycocyanin exhibits anti-inflammatory activity by inhibiting inflammation-related pathways. It also acts as a potent antioxidant, scavenging free radicals and protecting skin cells from oxidative stress [9], as well as from UVA-induced damage [10] and UVB-induced photoaging [11].

The aim of the present study was to investigate the therapeutic potential of phycocyanin, a natural pigment extracted by a green method from Spirulina platensis, to reduce inflammation.

II. MATERIALS AND METHODS

A. Investigated sample

Samples of Spirulina platensis (0.5 g) were weighed into 35 mL screw-capped centrifuge tubes and extracted with distilled water using three ultrasonic baths operating at frequencies of 36 kHz, 40 kHz, and 45 kHz for 1, 2, and 3 hours, respectively, at temperatures of 20 °C, 30 °C, and 40 °C. The obtained extracts were filtered through filter paper and used for subsequent analyses of the phycocyanin yield and purity index.

The results demonstrated that the highest purity of phycocyanin was achieved under extraction conditions of 40 kHz ultrasonic frequency, 30 °C temperature, and 2 hours extraction time [12].

B. Chemicals

The solution for injection of diclofenac sodium (Almiral®, Medochemie, Cyprus) was purchased from a pharmacy store. Histamine and λ –carrageenan were obtained from Sigma Aldrich and were of analytical grade. These reagents were dissolved in saline. The tested phycocyanin was dissolved in distilled water.

C. Animals

Male Wistar rats weighing 90 - 160 g were used. The animals were housed under standard laboratory conditions: a 12/12 h light/dark cycle, temperature 22 ± 1 °C, humidity 45%, and access to food and water ad libitum.

D. Histamine-induced paw edema

Forty male Wistar rats were divided into five groups (n = 8) and treated orally as follows: 1st group (control) – treated with distilled water (1 mL/100 g bw), 2nd group – treated with diclofenac sodium in a dose of 10 mg/kg bw, 3rd group – treated with 50 mg/kg bw phycocyanin, 4th group – treated with 200 mg/kg bw phycocyanin, and 5th group – treated with 300 mg/kg bw phycocyanin. The volume of each injection was 100 µL/100 g bw. One hour after the treatment, the animals received a subplantar injection of 100 µL of a 0.1% solution of histamine in saline into the right hind paw. Hind paw volume was measured immediately before histamine injection and at the 5th, 15th, 30th, 60th, 90th, and 120th min with a plethysmometer (Ugo Basile, Gemonio, Italy). The paw edema was calculated according to the formula:

Percentage of increase (%) = $[(V_n-V_0)/V_0] \times 100$, where (1)

V_n is the volume of the right hind paw registered after histamine injection at the n-th min;

V_0 is the volume of the right hind paw registered for the same animal before histamine injection.

E. Carrageenan-induced paw edema

Forty male Wistar rats were allocated randomly into five groups (n = 8) and treated orally. The rats of the 1st group (control) received distilled water (1 mL/100 g bw), and animals in the 2nd group received diclofenac sodium at a dose of 10 mg/kg bw. The experimental rats from the 3rd group received 50 mg/kg bw phycocyanin, the 4th group received 200 mg/kg bw phycocyanin, and the 5th group received 300 mg/kg bw phycocyanin. The injected volume was 0.1 mL/100 g bw. A subplantar injection of 0.1 mL of a 1% solution of degraded λ-carrageenan in saline was applied 1 h after treatment with the substances into the right hind paw. The paw volume was measured immediately before carrageenan injection and at the 1st, 2nd, 3rd, 4th, and 5th hour after the injection using a Plethysmometer apparatus (Ugo Basile, Gemonio, Italy).

Calculation of the paw edema was based on the formula (1) for calculating Percentage of increase (%), where V_n = the volume of the right hind paw measured after carrageenan injection at the n-th hour and V_0 = the volume of the right hind paw measured for the same rat before carrageenan injection.

F. Statistical analysis

Statistical analyses were conducted using SPSS version 17.0. The normality of data distribution was assessed with the One-sample Kolmogorov–Smirnov test. To compare groups, one-way ANOVA followed by the Bonferroni post hoc test was applied. The number of tested animals is given as n. Data are expressed as mean ± SEM, and differences were deemed statistically significant at $p < 0.05$.

III.RESULTS AND DISCUSSION

A. Effect of phycocyanin on histamine-induced paw edema

Phycocyanin showed well-defined anti-inflammatory effect in the model of histamine-induced paw edema (Fig. 1). The lowest dose of phycocyanin (50 mg/kg) caused a significant inhibition of the paw edema at the 15th min (27.70 ± 1.75 vs. 46.47 ± 6.33; $p < 0.05$), at the 60th min (31.66 ± 3.43 vs. 48.20 ± 4.79; $p < 0.05$), at the 90th min (26.47 ± 3.24 vs. 43.46 ± 5.36; $p < 0.05$), and at the 120th min of the experiment (22.70 ± 2.96 vs. 41.90 ± 4.85; $p < 0.01$) in comparison to the control group. A significant antiphlogistic activity was also observed in the group treated with phycocyanin at a dose of 200 mg/kg at the 15th min (27.54 ± 2.95 vs. 46.47 ± 6.33; $p < 0.05$), at the 30th min (34.57 ± 2.44 vs. 50.46 ± 4.33; $p < 0.05$), at the 60th min (27.57 ± 2.20 vs. 48.20 ± 4.79; $p < 0.01$), at the 90th min (25.84 ± 3.21 vs. 43.46 ± 5.36; $p < 0.05$), and at the 120th min (22.60 ± 3.21 vs. 41.90 ± 4.85; $p < 0.01$) after the histamine application when compared to controls. A significant anti-inflammatory effect was registered in the group treated with the highest dose of phycocyanin (300 mg/kg) at the 15th min (26.95 ± 3.86 vs. 46.47 ± 6.33; $p < 0.05$), at the 30th min (28.39 ± 4.40 vs. 50.46 ± 4.33; $p < 0.01$), at the 60th min (26.53 ± 4.23 vs. 48.20 ± 4.79; $p < 0.01$), at the 90th min (23.42 ± 3.84 vs. 43.46 ± 5.36; $p < 0.01$), and at the 120th min of the testing (21.62 ± 3.96 vs. 41.90 ± 4.85; $p < 0.01$) in comparison to controls (Fig. 1).

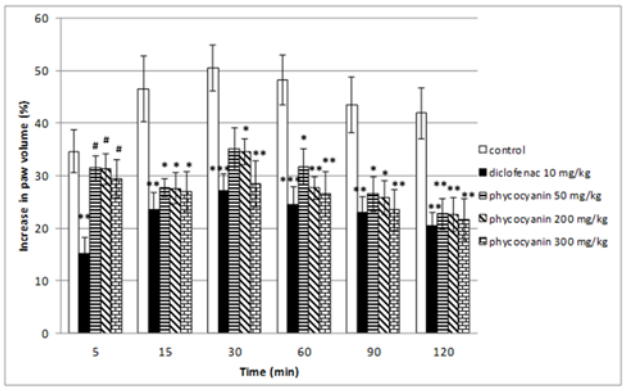

Figure 1. Effects of diclofenac and phycocyanin (50, 200, and 300 mg/kg bw) on paw edema induced by histamine in rats. *$p < 0.05$ vs. controls at the same time; **$p < 0.01$ vs. controls at the same time; ***$p \leq 0.001$ vs. controls at the same time; #$p < 0.05$ vs. diclofenac at the same time.

B. **Effect of phycocyanin on carrageenan-induced paw edema**

Phycocyanin in the three doses studied (50, 200, and 300 mg/kg bw) showed a well-defined anti-inflammatory effect with peak activity at the 5th hour after the application: 27.95 ± 5.85 for 50 mg/kg bw, 23.84 ± 3.49 for 200 mg/kg bw, and 19.77 ± 4.03 for the highest dose 300 mg/kg bw vs 66.07 ± 7.26, $p < 0.001$ when compared to controls. The effect was also present at the 4th hour for the three doses investigated: 50 mg/kg bw phycocyanin (30.59 ± 5.78 vs 58.14 ± 6.41; $p < 0.01$), 200 mg/kg bw phycocyanin (26.66 ± 3.71 vs 58.14 ± 6.41; $p \leq 0.001$), and 300 mg/kg bw phycocyanin (21.96 ± 4.25 vs 58.14 ± 6.41; $p < 0.001$) in comparison to controls. At the 3rd hour of the experiment, a significant decrease in the paw edema in comparison to control rats was registered after treatment with phycocyanin in doses 200 mg/kg bw (28.28 ± 3.67 vs 54.64 ± 6.34; $p < 0.05$) and 300 mg/kg bw (24.68 ± 4.54 vs 54.64 ± 6.34; $p < 0.01$) (Fig. 2).

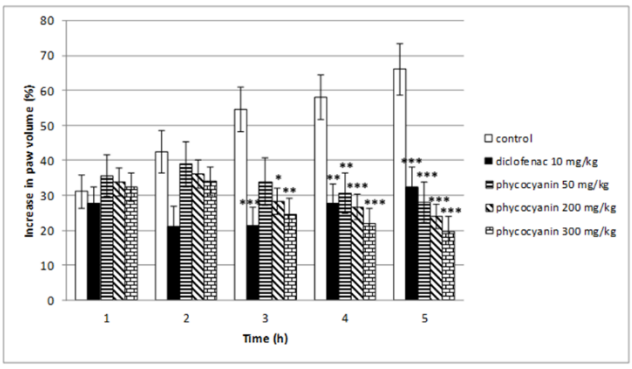

Figure 2. Effects of diclofenac and phycocyanin (50, 200, and 300 mg/kg bw) on paw edema induced by carrageenan in rats. *$p < 0.05$ vs. controls at the same time; **$p < 0.01$ vs. controls at the same time; ***$p \leq 0.001$ vs. controls at the same time.

We registered a well-defined anti-inflammatory activity of phycocyanin (50, 200, and 300 mg/kg bw p.o.) in two animal models. To study the initial phase of the inflammatory response, researchers commonly employ the histamine-induced inflammation model. In our study, phycocyanin demonstrated a notable dose-dependent anti-inflammatory effect in rats with histamine-induced rat paw edema. An inhibitory effect of phycocyanin on allergic inflammatory response was also reported by Remirez et al. (2002) [13]. The anti-allergic properties of phycocyanin were demonstrated in several experimental models, including ovalbumin-induced ear swelling in sensitized mice, skin reactions to histamine and compound 48/80 in rats, and histamine release from isolated rat peritoneal mast cells triggered by compound 48/80. Oral administration of phycocyanin (100 and 200 mg/kg bw p.o.) significantly and dose-dependently reduced key indicators such as edema, myeloperoxidase activity, and skin reactions. The results indicate that phycocyanin's ability to suppress the allergic inflammatory response is, at least partially, due to its inhibition of histamine release from mast cells [13].

A dose-dependent anti-inflammatory effect of phycocyanin was also presented in our experiments with carrageenan-induced rat paw edema. The latter is a widely used model for the evaluation of novel anti-inflammatory compounds and antioxidants. The antiphlogistic effect of phycocyanin in doses 50, 100, and 200 mg/kg bw p.o. is also demonstrated by Romay et al. in the same animal model [14]. These authors showed that the anti-inflammatory effect of phycocyanin does not rely on corticosteroid release, as it reduced paw edema caused by carrageenan equally in both intact and adrenalectomized rats under identical treatment conditions. On the other hand, its antioxidant and free radical scavenging abilities may play a role, at least partially, in mediating its anti-inflammatory effects [14]. Later Romay et al. observed a significant anti-inflammatory effect of phycocyanin (50-200 mg/kg p.o.) that reduced in a dose-dependent manner prostaglandin E_2 levels by moderate

inhibition of phospholipase [15]. The antiphlogistic effect of phycocyanin in animals was reported in many other studies previously [16]. Phycocyanin has outstanding antioxidant and anti-inflammatory activities, and can effectively inhibit various inflammatory diseases in the liver, bowel, lung, cardiovascular, and nervous systems [8].

Phycocyanin can affect inflammation through direct and indirect mechanisms. The direct anti-inflammatory effect involves the suppression of tissue inflammation via primary inflammatory TLR and NF-κB signaling pathways. Li et al. demonstrated that phycocyanin alleviates bleomycin-induced inflammation in wild-type mice, but has little to no effect in TLR-deficient mice, suggesting the involvement of the TLR2 signaling pathway in phycocyanin's anti-inflammatory activity [17]. Similarly, Liu et al. reported that pretreatment with phycocyanin inhibits the TLR2/NF-κB signaling pathway and leads to a reduction in IL-6 and TNF-α levels [18]. Phycocyanin also appears to exert a comparable effect on TLR4, where it suppresses the expression of pro-inflammatory cytokines by blocking the TLR4-mediated NF-κB pathway [19]. Research on pulmonary fibrosis has shown that phycocyanin can suppress fibrosis progression and decrease tissue inflammation by modulating the TGF-β/NF-κB pathway [18]. Alzokaky et al. reported that pretreatment with phycocyanin significantly lowered the expression of high mobility group protein B1 (HMGB1) by inhibiting the NLRP3/NF-κB pathway. This was accompanied by reductions in oxidative stress markers, IL-1β, TNF-α, and ulcer index values, thereby offering protective effects against gastric ulcers [20]. Beyond disease-specific models, phycocyanin also influences immune cell activity, particularly in macrophages. Hao et al. demonstrated that phycocyanin reduced inflammatory cytokine expression in LPS-stimulated macrophages by inhibiting NF-κB activation, thereby attenuating the inflammatory response [21].

The indirect anti-inflammatory effect of phycocyanin is related to its antioxidant effect and its influence on apoptosis. Liu et al. investigated liver injury caused by X-ray exposure and found that phycocyanin activates the Nrf2 signaling pathway in mice, thereby mitigating oxidative stress induced by radiation [22]. Kim et al. reported that phycocyanin promotes the synthesis of hemeoxygenase-1 (HO-1) via the PKC α/β II–Nrf2/HO-1 signaling cascade, protecting primary skin cells from UV-induced apoptosis [23]. Gao et al. demonstrated that phycocyanin activates Nrf2 and upregulates HO-1 expression, thereby preventing methylglyoxal-induced mitochondrial-dependent apoptosis in INS-1 pancreatic α cells [24]. Leung et al. observed that phycocyanin treatment led to a reduction in the pro-apoptotic protein caspase-3 and an increase in the anti-apoptotic protein Bcl-2 in lung tissue, thereby alleviating LPS-induced pulmonary inflammation [25]. Similarly, Kim et al. demonstrated that phycocyanin protects against UVB-induced apoptosis by lowering the expression of p53 and Bax and inhibiting caspase-3 activity [23]. These findings suggest that phycocyanin can modulate apoptotic signaling pathways by suppressing caspase-3 activation, enhancing the expression of anti-apoptotic proteins such as Bcl-2, and ultimately reducing inflammation-induced cellular apoptosis in tissues.

IV. CONCLUSIONS

The present study demonstrated that phycocyanin extracted from Spirulina platensis exhibits a significant anti-inflammatory effect in both histamine- and carrageenan-induced rat paw edema models. The results revealed a clear dose-dependent inhibition of inflammation, with the most pronounced activity observed at higher phycocyanin concentrations (200–300 mg/kg bw). The effectiveness of phycocyanin was comparable to that of the reference non-steroidal anti-inflammatory drug diclofenac sodium, indicating its strong pharmacological potential.

The anti-inflammatory action of phycocyanin is likely associated with the modulation of key molecular pathways, including TLR/NF-κB and Nrf2/HO-1, which are involved in the regulation of oxidative stress and inflammatory mediators. These findings support previous evidence that phycocyanin exerts its biological effects through both direct suppression of pro-inflammatory cytokines and indirect antioxidant mechanisms.

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