

C-Phycocyanin derived from *Spirulina maxima* attenuates the symptoms of psoriasis in mouse models

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Abstract

Background: Psoriasis is a chronic autoimmune disease caused by the abnormal proliferation of keratinocytes in the epidermis. The efficacy of c-phycoerythrin, a photosynthetic pigment isolated from *Spirulina maxima*, was assessed via histological examinations, and anti-inflammatory properties were investigated in mouse models of imiquimod-induced psoriasis (BALB/C-nu and BALB/C).

Result: C-Phycocyanin lowered epidermal thickening, as well as immune cell clustering in the dermis. Furthermore, C-phycoerythrin modulated the levels of inflammatory cytokines (tumor necrosis factor- α , interleukin (IL)-6, cyclooxygenase-2, IL-1 β) in the BALB/C-nu mouse model and psoriasis-related cytokines (IL-17 α , interferon-gamma, calcitonin gene-related peptide) in BALB/c mice.

Conclusion: We show that C-Phycocyanin could be developed as a natural pharmaceutical against psoriasis.

1. Background

Psoriasis is a chronic autoimmune disease characterized by the abnormal proliferation of keratinocytes in the epidermis [1]. Although the exact cause of psoriasis remains unknown, immune factors, environmental factors, infection, and psychological stress have been implicated in its pathogenesis. [2–6]. Plaque psoriasis or psoriasis vulgaris is the most common type observed worldwide. Plaque psoriasis is typically characterized by the presence of plaques with silver scales. As a symptom of psoriasis, the epidermal granular layer disappears and the cells in the stratum corneum retain their nuclei. The stratum corneum becomes thicker and unaligned. Hence, owing to these changes, the epidermis loses its role as a moisture barrier [7].

Several drugs demonstrating anti-inflammatory, antihistaminic, and antioxidant properties have been used to treat psoriasis [8–10]. Despite the numerous drugs and treatments available, natural pharmaceutical products or treatment strategies are gaining momentum, as synthetic drugs could have adverse effects on the psoriatic tissue where immune cells are locally activated [11–13].

C-Phycocyanin (C-PC), a natural pigment from cyanobacteria, is known to possess potent antioxidant, anti-inflammatory, and antihistaminic properties [19]. Thus, C-PC has widely been investigated as a bioactive pharmaceutical compound for several diseases, including cancer, central nervous system (CNS) injury, or stroke [20–22]. Especially, in skin disorders, C-PC has demonstrated efficacy in atopic dermatitis, as well as allergic inflammation models [23]. Nevertheless, C-PC has rarely been utilized in a psoriasis model.

In psoriasis, immune dysfunction involves the interaction of immune and non-immune cells. Currently, there is no objective parameter to measure the severity of psoriasis, but several studies have reportedly measured the severity of psoriasis by monitoring the levels of various cytokines [14–18]. In this study, we evaluated the levels of pro-inflammatory and T cell-related cytokines, including tumor necrosis factor

(TNF)- α , interleukin (IL)-17, IL-6, IL-1b, interferon (IFN)- γ , cyclooxygenase (COX)-2, and calcitonin gene-related peptide (CGRP) for monitoring the severity of psoriasis.

Additionally, the activity of C-PC was assessed using a mouse model (BALB/c-nu, BALB/c) of psoriasis, successfully established after treatment with imiquimod cream, and the efficacy of C-PC was assessed by histological and molecular analyses.

2. Methods

2.1 Materials

Spirulina tablets cultured from lava seawater were donated by KIOST (Gyeonggi-do, Korea). Piperazine, sodium chloride, and C-PC (*spirulina* sp.) were purchased from Sigma Aldrich (USA). Tris(hydroxymethyl)aminomethane (Tris), ethylenediaminetetraacetic acid (EDTA), disodium salt dihydrate, and sucrose were purchased from USB Corporation (USA). Ammonium sulfate and hydrochloric acid were purchased from DaeJung Chemical Co. (South Korea) and Samchun Chemical Co. (South Korea), respectively. The following methodologies and relevant kits were used in this study: centrifugation (Supra 25K, Hanil, South Korea); anion exchange chromatography (HiTrap Q HP, GE Healthcare, USA); dialysis (MEMBRA-CEL MC18 X 100 CLR; Serva, Germany); AKTA start purification system with Frac30 fraction collector (GE Healthcare, USA); spectroscopy with a microplate reader, equipped with a 50 W xenon flash lamp (Varioskan LUX, Thermo Scientific, USA); RNeasy Mini kit plus (Takara Bio, Japan); QuantiFasT Reverse Transcription kit (Qiagen, Germany); Rotor-Gene Q PCR (Qiagen, Germany); ultra-centrifugation (Vivaspin 500, MWCO 10000, Sartorius Germany)

2.2 Extraction and purification of the c-phycoerythrin complex from *Spirulina*

To obtain C-PC, we utilized *Spirulina* maxima from Jeju (Republic of Korea). The cell wall was lysed using a lysis buffer (1 M Tris (pH 8.0), 0.5 M EDTA, and 20% (w/v) sucrose) and 50 mM piperazine buffer (pH 6.0) for 1 h at 4°C. Cell debris was removed by centrifugation at 10000 $\times g$, for 15 min at 4°C. After removing the proteins precipitated at low concentrations of ammonium sulfate (0–30% (w/v)), the proteins in the supernatant were precipitated using high concentrations of ammonium sulfate (30–50% saturation) as previously described [24]. Then, precipitated proteins were dialyzed and further purified using anion exchange chromatography. To elute C-PC, 0.05 M piperazine (pH 6.0) containing 0.3 M sodium chloride was used. Chromatography was performed using the AKTA start purification system with the Frac30 fraction collector.

2.3 The psoriatic mouse model

The *in vivo* efficacy of C-PC was evaluated using female BALB/c-nu and female BALB/c mice (Orient Bio, Korea). The study was approved by the Institutional Animal Care and Use Committee of Inha University (Incheon in South Korea, Approval Number, INHA 150924-381). Animals were housed in a climate-controlled environment (25 \pm 2°C, 45% relative humidity) with a 12 h light/dark cycle and provided *ad libitum* access to food and water. The animals of each type were divided into seven groups (Table. 1). Each group has 3 animals and a total of 21 mouse of each species were used. BALB/c mice were

depilated using a hair removal cream. For 12 days, 5% imiquimod cream was applied every morning to the dorsal skin of the mice. From the 7th day, C-PC was administered to the remaining four groups (Group \square , Group \square , Group \square , Group \square) similar to the positive control, once a day in the evening. The negative control group was treated with the buffer used to purify the C-PC and maintained as the induced disease control group. BALB/c-nu and BALB/c mice were euthanized on the 12th day using CO₂, and the skin, spleen, and ears were collected from each group.

2.4 Measurement of inflammation severity scores

The severity of inflammation and redness was classified based on the presence of scaling, thickening, lesions, and erythema on the dorsal and ear skin. The score was individually determined for all groups from 0 to 9 as follows: 0; none, 1-3; slight, 4-6; moderate, 7-9; severe.

2.5 Skin morphology (H&E staining) and measurement of epithelial thickness

Samples of the dorsal skin were fixed using 4% neutral buffered formalin. The samples were fixed onto a 15 mL Falcon tube, and for the dehydration of the fixed sample, each sample was dipped in a 30% sucrose solution in a 24-well plate overnight. On immersing the samples, the procedure was changed to a 50% sucrose solution. After generating the block using optimal cutting temperature compound (O.C.T. compound), the samples were cut to a thickness of 40 μ m using a microtome. To remove O.C.T, the samples were washed with distilled water, followed by immersion in a hematoxylin solution for 8 min. Using distilled water in a squeeze bottle, the samples were washed until the dye was released. After eosin staining for 1 min, the samples were washed until the dye was released. The cover glass was placed on the sample and observed using a microscope (Micros, Austria). Epithelial thickness was measured using ImageJ (ImageJ 1.49V).

2.6 Quantitative real-time PCR (qRT-PCR)

The mRNAs from the epidermis, ear, and spleen samples of mice in which psoriasis was induced were quantified using qRT-PCR according to the manufacturer's instructions. Each sample was homogenized, and total RNA was purified using a RNeasy MiNi kit plus. cDNA was synthesized using a Transcript All-in-One First strand cDNA synthesis SuperMix (TransGen, Germany). qRT-PCR was performed using the QuantiFast SYBR Green PCR Kit (QIAGEN, Germany); Rotor-Gene Q PCR (QIAGEN, Germany) was used to quantify the expression of markers.

2.7 Statistical analysis

All experiments were repeated thrice to validate the reliability of the results obtained. The relationship between the standard deviation and mean value of the experimental data was confirmed by statistical analysis using the *t*-test in the SigmaPlot program.

(* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$)

3. Results

Both spleen and ear obtained from BALB / c-nu were used for qRT-PCR analysis, and skin tissue obtained from both species was used for Histological analysis and qRT-PCR analysis.

3.1 Assessment of C-PC in the BALB/c-nu mice psoriasis model

To induce plaque psoriasis in BALB/c-nu mice, imiquimod cream was applied. These mice exhibited characteristic scaling, redness, and thickness with silver scales. In this study, mometasone furoate (Novasone™ cream), used as a positive control, eliminated silver scales. Similarly, C-PC eliminated the presence of silver scales from the psoriatic skin mice in which psoriasis was induced (Fig. 1a). With respect to the severity scores, the experimental group with imiquimod-induced psoriasis demonstrated higher scores in both ear and dorsal skin when compared to the experimental group treated with 1 µg and 5 µg C-PC. (Fig. 2a). These results showed a more positive than effect of mometasone furoate. However, the image and severity scores were negatively affected when the animals were treated with more than 10 µg C-PC.

3.1.1. Downregulation of IL-6, IL-1b, COX-2, and TNF-α mRNA expression in BALB/c-nu mice

IL-1b is expressed in activated macrophage cells and is involved in cell proliferation, differentiation, and apoptosis. Following the induction of psoriasis, IL-1b levels increase, which then induce the expression of COX-2 and COX-2 in psoriasis [15, 17]. Furthermore, the levels of the pro-inflammatory factor, IL-6, and inflammatory factor, TNF-α, are reportedly increased following the induction of psoriasis [14]. We treated imiquimod-induced psoriatic BALB/c-nu with C-PC and mometasone, and collected the dorsal and ear skin, as well as the spleen. After isolating the tissue RNA, qRT-PCR was performed to measure the expression of four cytokines (IL-6, IL-1b, COX-2, and TNF-α). In the ear skin, the levels of TNF-α continuously decreased as the C-PC concentration increased; COX-2 expression was also decreased (Fig. 5). However, treatment with 10 µg C-PC marginally increased the expression of TNF-α and COX-2 when compared to the experimental group treated with 5 µg C-PC. Similarly, for tissues derived from the spleen and dorsal skin, qRT-PCR demonstrated that the expression of IL-1b, COX-2, IL-6, and TNF-α decreased following C-PC treatment (Fig. 5).

3.1.2. Histological analysis of C-PC in the BALB/c-nu psoriasis model

Following the induction of psoriasis, the stratum corneum thickened, with cell clusters observed in the epidermal layer [7, 25]. In normal skin tissue (sham), the epidermis consists of 2–3 epithelial layers, with a stack of stratum granulosum, stratum spinosum, and stratum basale; the dermis is located below the epidermis, and is composed of hair follicles, sebaceous glands, and the extracellular matrix. However, tissues from the imiquimod-treated animals exhibited 4–16 thickened epidermal layers (Fig. 3). In the sham, psoriasis, and mometasone-treated groups, the epidermal thickness was 33.534 µm, 88.727 µm, and 31.338 µm, respectively (Table. 2). The C-PC-treated group demonstrated an epidermal thickness that was comparable to that observed in the mometasone-treated group; however, histological differences were not significant among C-PC treated samples.

3.2 Assessment of C-PC in the BALB/c mouse psoriasis model

Psoriasis was induced in BALB/c mice using imiquimod cream. Similar to that in the BALB/c-nu mice, the

degree of redness and scaling was lowered in all groups treated with mometasone and C-PC when compared to the imiquimod-treated group (Fig. 1b). However, in the 10 µg C-PC treated group, psoriasis symptoms were more severe than those observed in the imiquimod-treated group. Similar scores were observed in terms of the severity of inflammation (Fig. 2b).

3.3.1. Downregulation of IL-1b, COX-2, TNF-α, IL-17a, IFN-γ, and CGRP mRNA expression in BALB/c mouse

Reportedly, the expression of COX-2, IL-1b, TNF-α, IFN-γ, IL-17a, and CGRP mRNA is known to increase in psoriasis [14-17]. In the BALB/C psoriasis model, the negative group treated with imiquimod demonstrated an increased expression of all six factors when compared with the sham and positive groups. The groups treated with 1 µg, 2 µg, and 5 µg C-PC showed a similar or more effective decrease in COX-2 and IL-1b expression when compared with the positive group (Fig. 6). Following treatment with 1 µg C-PC, the expression of TNF-α and CGRP was lowered compared to that observed in the sham group; however, the other C-PC concentrations failed to effectively decrease the expression of these molecules. IFN-γ expression was decreased in the mometasone-treated group, but no significant change was observed in the C-PC treated groups. In the 1 µg, 2 µg, and 5 µg C-PC treated groups, the expression of IL-17a was altered to levels observed in the sham group. Following treatment with 10 µg C-PC, the expression of all factors was higher than that observed in the negative group.

3.3.2. Histological analysis in C-PC-treated BALB/c psoriasis model

In the sham, psoriasis, and mometasone-treated groups, the epidermal thickness was 23.86 µm, 57.06 µm, and 38.98 µm, respectively (Table.3). In the 1 µg treated C-PC group, the results were similar to those observed in the mometasone-treated group (Fig. 4). However, treatment with more than 2 µg of C-PC demonstrated minimal effects on the thickness of the epidermal layer.

4. Discussion

Psoriasis is characterized by abnormally proliferating keratinocytes induced by T lymphocytes; this condition is associated with atopic dermatitis. Previously, C-PC has been demonstrated to have antioxidant and anti-inflammatory properties [26, 27]. Hence, the present study was performed to assess whether C-PC is effective in an animal model of psoriasis. We performed histological and inflammatory investigations to elucidate the positive effects of C-PC.

In histological findings, the psoriasis mouse model showed typical epidermal thickening, as well as plaques of silver scales. In the C-PC treated model, the removal of silver scales was explicitly observed. A dramatic decrease in epidermal thickness is a positive indication of C-PC efficacy against psoriasis. The abnormal proliferation of keratinocytes in the epidermal layer causes psoriatic, epidermal thickening. Thus, it can be postulated that C-PC modulates keratinocyte proliferation. In the dermis, psoriasis is characterized by a cluster of immune cells. In this study, the cell clusters in the dermis of the psoriasis model comprised immune cells. Notably, C-PC works well in the dermal layer of psoriasis, as demonstrated by the reduced number of immune cells when compared with those observed in the psoriasis model (Fig. 3, 4).

With respect to the inflammatory findings, the psoriasis model demonstrated elevated expression of all 6

factors (IL-1b, COX-2, TNF- α , IL-6, CGRP, IL-17a) when compared with the sham group. In BALB/c-nu mice, the levels of these inflammation-related factors tended to decrease as the C-PC concentration increased. In BALB/c-nu mice with FOXP1 gene knockout, the T cell-mediated response remains incomplete. Therefore, in the BALB/c-nu psoriasis model, the anti-inflammatory effect of C-PC is expected to lower the expression of inflammatory factors, thereby alleviating psoriatic symptoms. Conversely, in the BALB/c mouse model, in which the T cell-mediated response operates normally, C-PC demonstrates more than just an anti-inflammatory effect. Here, C-PC promoted the production of IFN- γ from T cells, with the generated IFN- γ increasing the activity of immune cells, including macrophages [29]. However, considering the decreased expression of several other inflammatory factors, inflammatory factors associated with psoriasis could be lowered to normal levels following C-PC treatment at an appropriate concentration.

5. Conclusion

In the present study, the potential efficacy of C-PC to treat skin psoriasis was investigated using a mouse model and analyzing tissue histology and mRNA expression levels of inflammatory factors. We successfully induced psoriasis in both models, presenting characteristic silver scales, a thickened epidermis, and clustered immune cells in the dermis. C-PC treatment resulted in silver scale removal, reduced epidermal thickness, and a reduced number of immune cells in the dermis. Furthermore, C-PC modulated the mRNA expression of inflammatory factors. These results demonstrated the potential application of C-PC as a natural pharmaceutical agent against psoriasis.

6. Abbreviations

C-Phycocyanin (C-PC)

central nervous system (CNS)

tumor necrosis factor- α (TNF- α)

interleukin-6 (IL-6)

cyclooxygenase-2 (COX-2)

interleukin-1b (IL-1b)

interleukin-17a (IL-17a)

interferon-gamma (IFN- γ)

calcitonin gene-related peptide (CGRP)

7. Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

SYJ performed research and analyzed data together with JP, SJY, YJC and JYJ. YJY and HSS supervised the study. SYJ wrote the article. All authors had full access to all data, read and approved the final manuscript

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Tables

Animal experiment groups

Group No.	Treated sample
Group 1	Healthy mice (sham)
Group 2	Positive control (mometasone)
Group 3	Negative control (0 μg , disease induced)
Group 4	purified C-PC (1 μg)
Group 5	purified C-PC (2 μg)
Group 6	purified C-PC (5 μg)
Group 7	purified C-PC (10 μg)

Table 1. The 7 groups used in BALB/c-nu and BALB/c mouse model test. Each group has 3 animals

BALB/c-nu Epithelium thickness (μm)

Sham	Positive (momentasone)	Negative (Non-treated)	1ug C-PC	2ug C-PC	5ug C-PC	10ug C-PC
17.01	18.081	132.428	62.294	32.587	28.966	65.934
28.387	19.471	90.527	72.43	75.137	29.885	58.657
71.857	22.728	82.63	57.937	47.984	47.07	69.519
20.684	38.933	78.081	49.972	37.124	36.219	70.243
29.551	57.476	59.969	41.283	56.129	31.695	49.264
33.53	31.34	88.727	56.78	49.79	34.77	62.72

Table 2. Measurement of epidermis thickness in BALB/c-nu mouse model.

BALB/c Epithelium thickness (μm)						
Sham	Positive (momentasone)	Negative (Non-treated)	1ug C-PC	2ug C-PC	5ug C-PC	10ug C-PC
23.985	38.451	70.779	41.1	64.598	40.383	62.367
30.855	55.066	59.174	41.858	52.417	58.119	67.751
26.586	39.957	45.346	33.309	39.796	71.128	45.251
15.99	34.009	55.388	39.037	55.856	41.153	52.197
21.895	27.42	54.603	62.099	53.182	55.79	41
23.86	38.98	57.06	43.48	53.17	53.31	59.45

Table 3. Measurement of epidermis thickness in BALB/c mouse model.

Figures

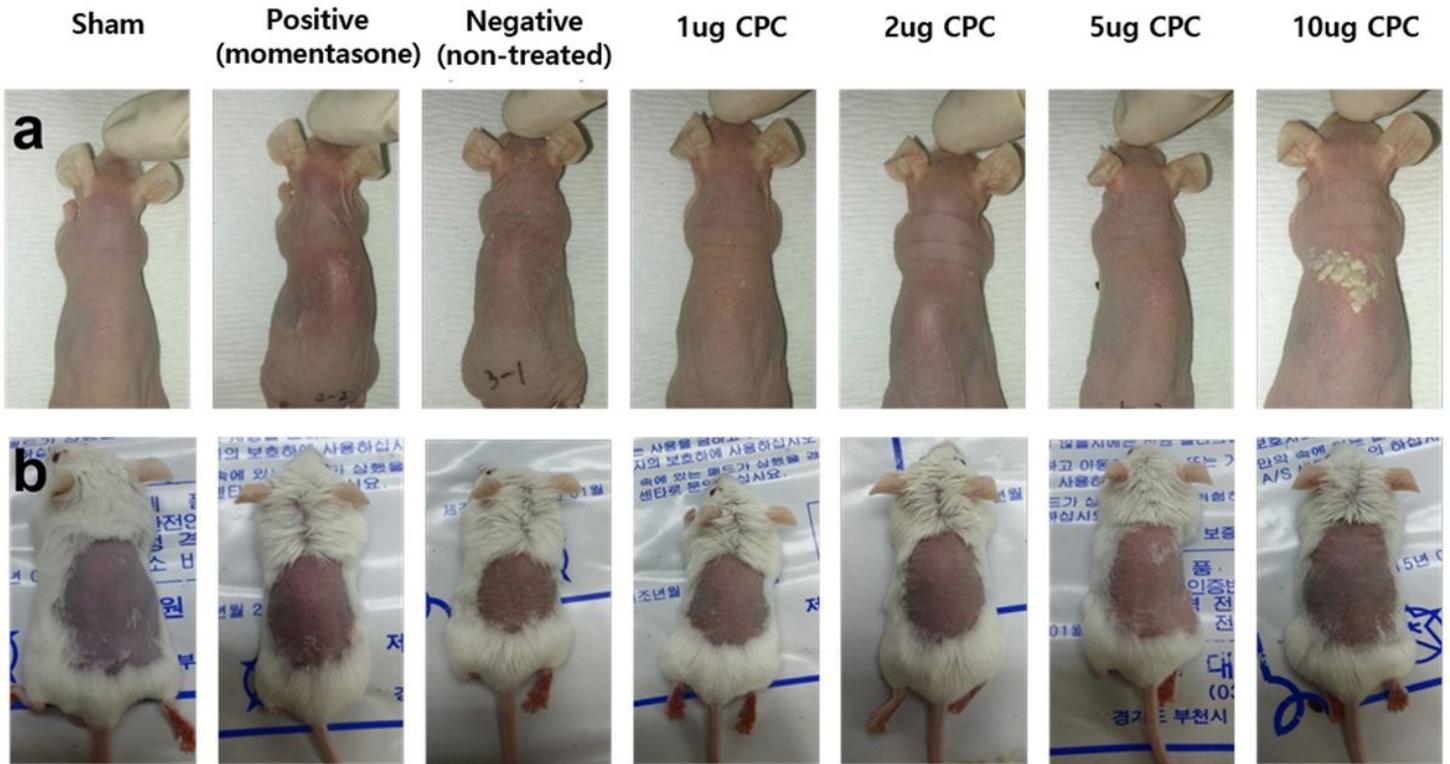


Figure 1

In vivo test images of psoriasis mouse models for sham, mometasone, imiquimod, and C-PC, respectively; (a) BALB/c-nu (b)BALB/c

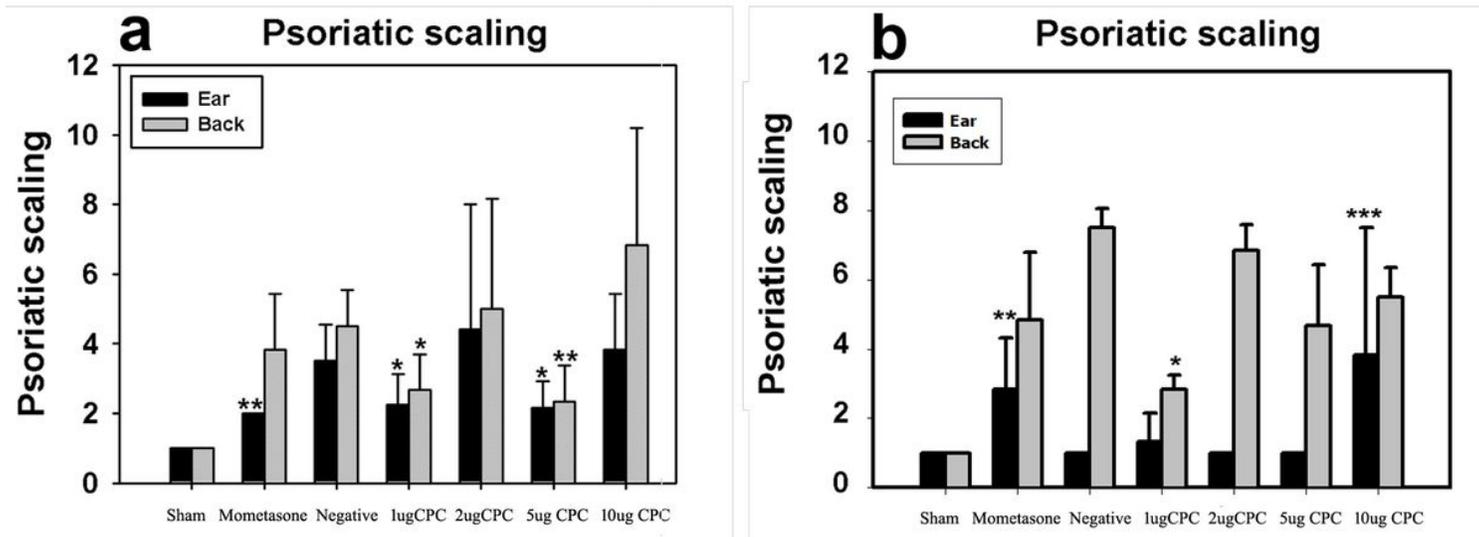


Figure 2

Measurement of inflammation severity scores on the ear and dorsal skin; (a) BALB/c-nu (b) BALB/c

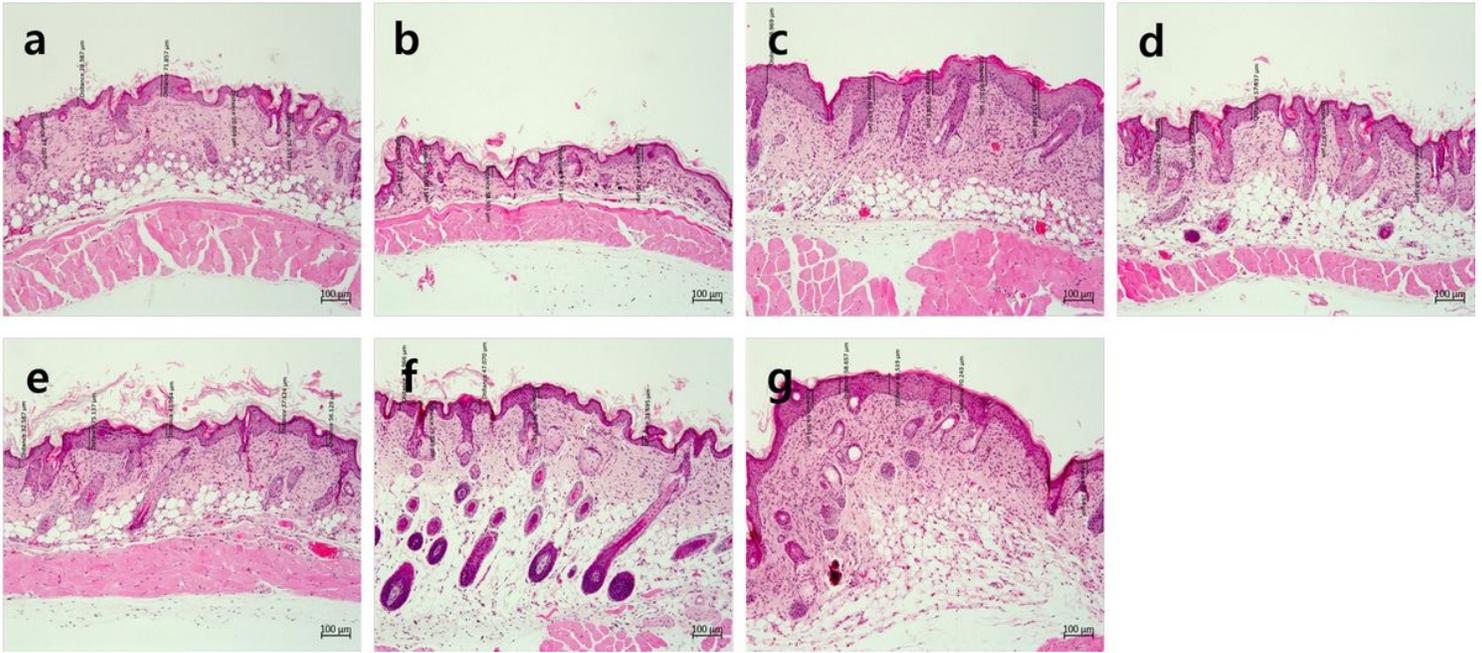


Figure 3

Histological evaluation of C-PC in BALB/c-nu mice with psoriasis ; (a) Sham, (b) Positive (mometasone), (c) Negative (non-treated), (d) 1 µg C-PC, (e) 2 µg C-PC (f) 5 µg C-PC, and (g) 10 µg C-PC

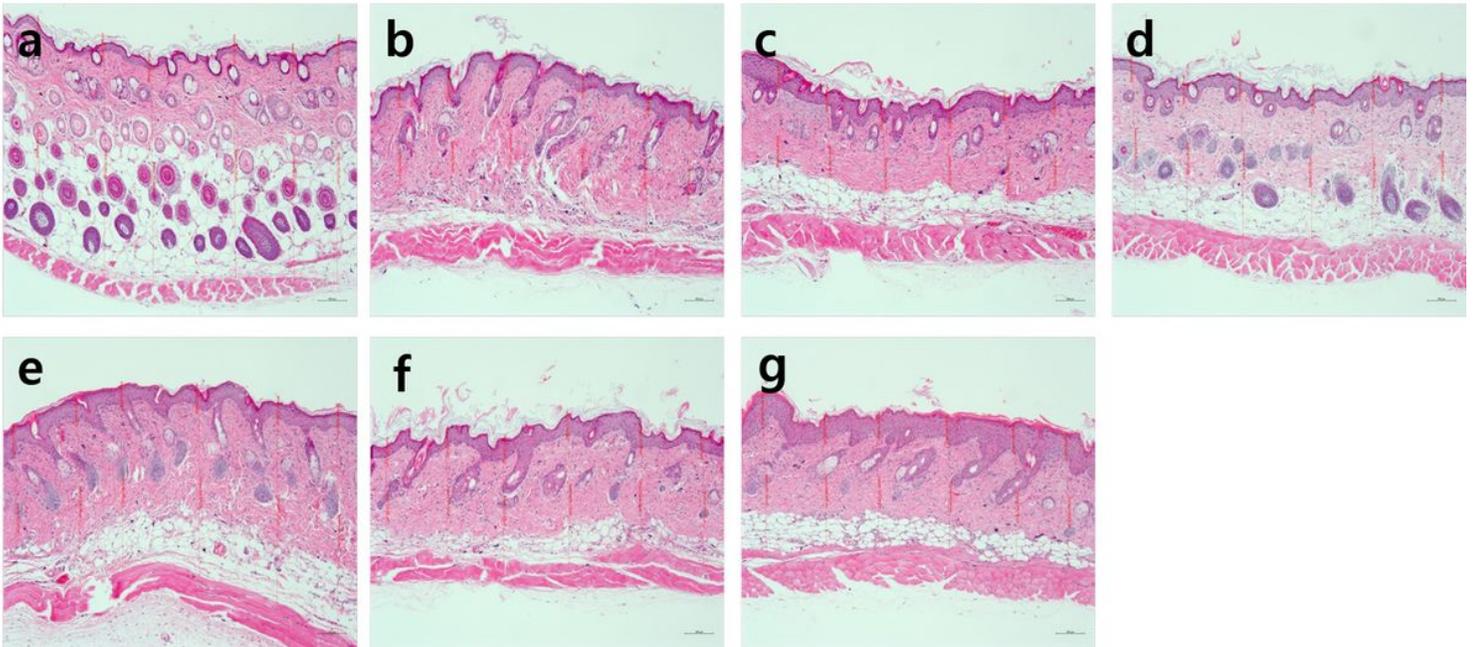


Figure 4

Histological evaluation of C-PC in psoriasis induced in BALB/c mice; (a) Sham, (b) Positive (mometasone), (c) Negative (non-treated), (d) 1 µg C-PC, (e) 2 µg C-PC, (f) 5 µg C-PC, and (g) 10 µg C-PC

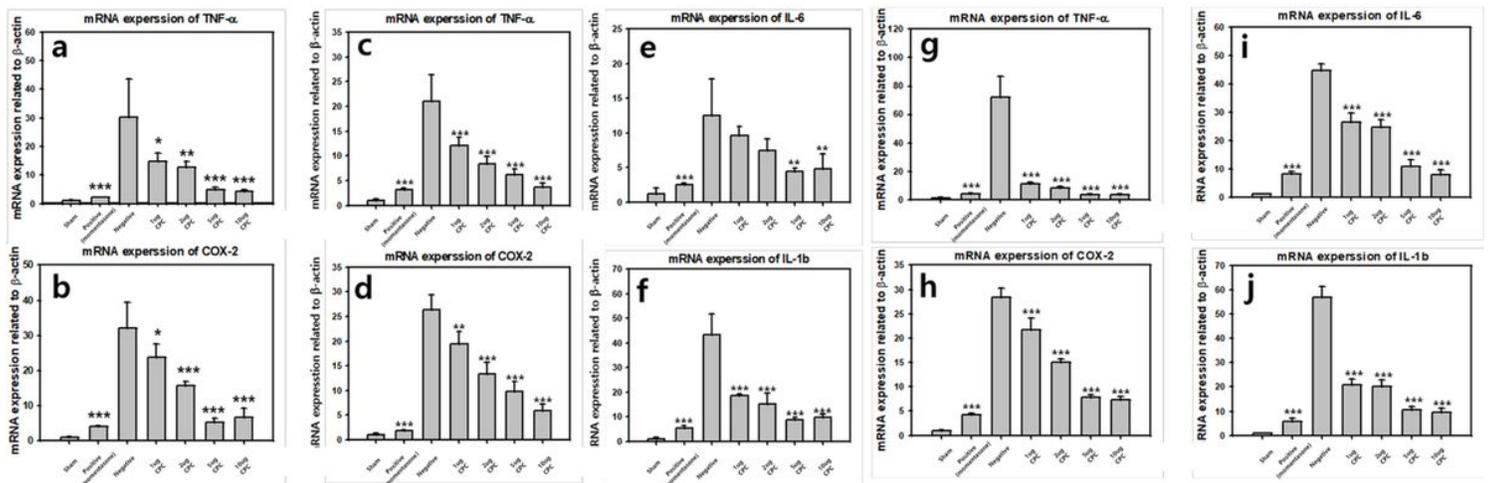


Figure 5

Expression of inflammatory factors in the ear, dorsal surface, and spleen of BALB/c-nu; (a, b) Expression of TNF-α and COX-2 in ear skin tissue. (c, d, e, f) Expression levels of TNF-α, COX-2, IL-6, and IL-1β in the dorsal skin tissue (g, h, i, j) Expression of TNF-α, COX-2, IL-6, and IL-1β in the spleen.

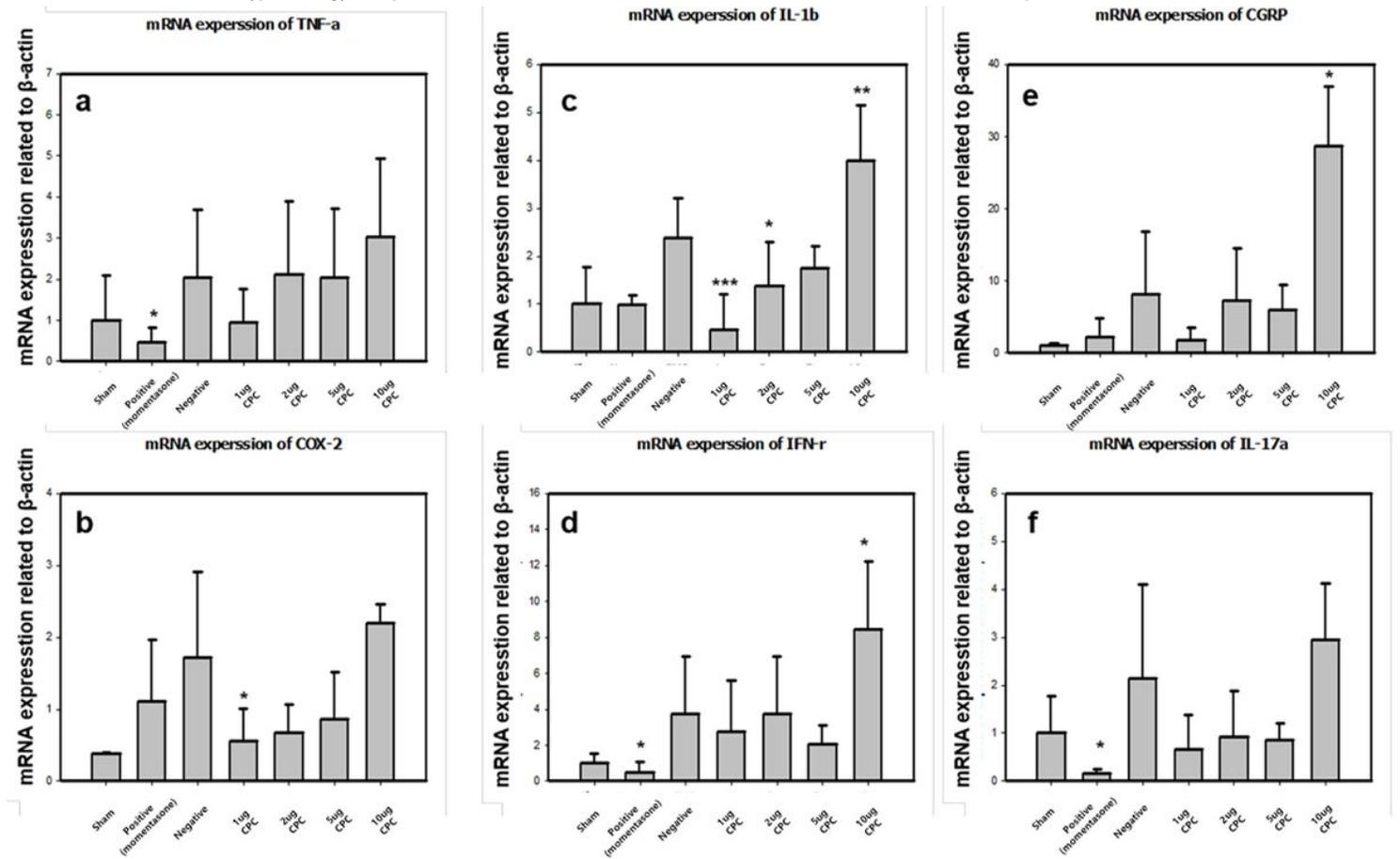


Figure 6

Expression of inflammatory factors present in the dorsal skin of BALB/c; (a) TNF- α , (b) COX-2, (c) IL-1 β , (d) IFN- γ , (e) CGRP, and (f) IL-17a

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