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ORIGINAL RESEARCH

Enhancement of Psoriasis Treatment by Phellodendri Chinensis Cortex Carbon Dots (PCC-CDs) Through Modulation of the HMGB1/TLR4/MAPK/NF-κB Pathway

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Background: Psoriasis is a chronic, debilitating inflammatory skin disorder mediated by the immune system. It is characterized by excessive keratinocyte proliferation and abnormal differentiation, leading to symptoms that significantly impair the quality of life of affected individuals. Despite extensive research, no effective drugs are currently available to completely inhibit the progression of psoriasis.
Purpose: This study aims to explore the therapeutic potential and underlying mechanisms of Phellodendron chinense charcoal carbon dots (PCC-CDs) in treating psoriasis. PCC-CDs have recently garnered attention due to their sustained anti-inflammatory properties and unique bioavailability.
Methods: This study explores the therapeutic potential and underlying mechanisms of PCC-CDs in psoriasis treatment via detailed pharmacological experiments in an imiquimod (IMQ)-induced mouse model, including topical PCC-CDs application, inflammatory mediator detection, histopathological assessment of tissue damage, and transcriptomic as well as molecular biology analyses focusing on the modulation of the HMGB1/TLR4 and MAPK/NF-κB inflammatory signaling pathways.
Results: In the IMQ-induced mouse model, PCC-CDs effectively suppressed the levels of inflammatory mediators and reduced histopathological damage. Molecular analyses revealed that PCC-CDs may exert their therapeutic effects by modulating the inflammatory response mediated by the HMGB1/TLR4 pathway, primarily through inhibiting protein expression in the MAPK/NF-κB signaling cascade. The application of PCC-CDs resulted in a significant reduction in psoriasis-like symptoms in IMQ-induced mice, including marked improvements in erythema, scaling, and pruritus.
Conclusion: PCC-CDs offer a promising new approach to the clinical management of psoriasis. Their ability to provide sustained anti-inflammatory effects and distinctive bioavailability makes them a potential candidate for further development as a therapeutic agent. This study highlights the importance of PCC-CDs in modulating key inflammatory pathways, offering hope for improved treatment options for individuals suffering from psoriasis.
Keywords: psoriasis, phellodendron chinense charcoal carbon dots spray, HMGB1, inflammatory response, pharmacological mechanisms

Introduction

Psoriasis treatments, including topical medications and phototherapy, effectively relieve symptoms and improve quality of life.[1,2] However, these conventional approaches may cause resistance and adverse effects.[3] Biologics are commonly

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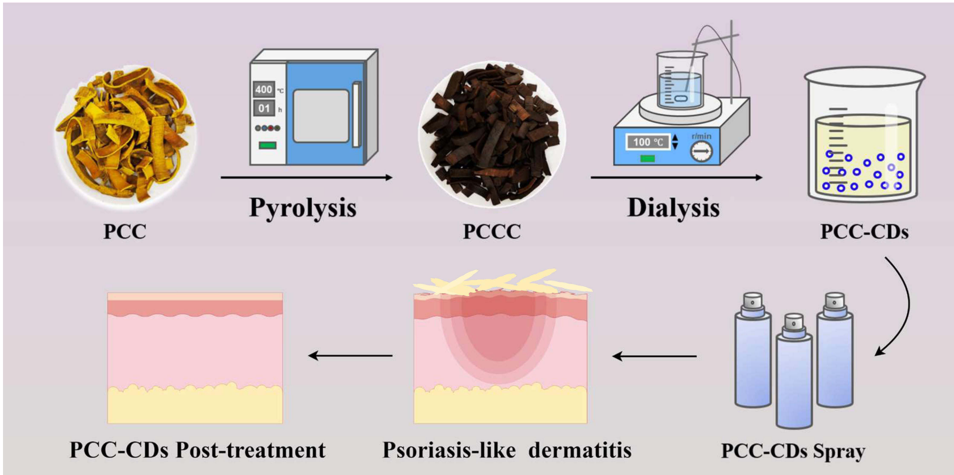
Graphical Abstract



used to treat moderate to severe psoriasis, but they are associated with side effects such as an increased risk of infection and reactions at the injection site.[4–6] These side effects can lead to treatment interruptions, which impact patient adherence and long-term outcomes.[7,8] Janus kinase (JAK)/signal transducer and activator of transcription (STAT) inhibitors are emerging as targeted small-molecule therapies that offer an alternative treatment for moderate-to-severe cases by blocking proinflammatory cytokine signaling, with oral administration improving convenience compared to injectable biologics.[9,10] Nevertheless, they still carry safety concerns, including the risk of infection, cutaneous adverse events and potential cardiovascular or hematological risks, which require long-term monitoring.[11–13] Therefore, there is an urgent need to develop new therapies that address the unmet needs of existing treatments, including biologic-related injection reactions and JAK inhibitor-associated safety issues.

Phellodendri Chinensis Cortex (PCC) was first documented in the "Shennong's Classic of Material Medica" and is widely used in dermatology for its heat-clearing, dampness-drying, detoxifying, and anti-inflammatory properties.[14,15] Documentation of the using of PCC charcoal in treating skin diseases has persisted for thousands of years. In traditional Chinese medicine (TCM), skin diseases are often associated with damp-heat, blood heat, and toxic pathogens.[16] PCC, being cold in nature and bitter in taste, effectively eliminates internal damp-heat, reducing inflammation and scaling in conditions such as eczema, dermatitis, and psoriasis.[17,18] In TCM prescriptions, PCC is frequently used as a principal or adjunctive herb in formulas that clear heat, detoxify, cool the blood, and moisturize the skin, such as "Longdan Xiegan decoction" or "Huanglian Jiedu decoction".[19–21] It plays a unique role in regulating skin inflammation and improving lesions, and is commonly used to alleviate symptoms like itching, erythema, and scaling in psoriasis and atopic dermatitis.[22–24]

Nanotechnology has recently opened new avenues for modernizing and refining the treatment of TCM.[25,26] Transforming herbal medicines into nanoparticles enhances drug bioavailability, targeting, and stability while minimizing side effects.[27,28] This method aligns well with multi-component, multi-target therapeutic principles of TCM, offering significant potential for innovative applications of Chinese herbal medicine. Our previous research has found that intraperitoneal administration of PCC carbon dots (CDs), enhances its hemostatic, astringent, and anti-inflammatory effects, and demonstrate notable anti-psoriatic effects in imiquimod (IMQ)-induced mouse models, likely through the regulation of macrophage polarization.[29] These findings position PCC-CDs as a promising avenue for psoriasis treatment. Topical administration bypasses the systemic side effects of oral medications, providing a safer and more effective option for patients.[30,31] Therefore, we prepared a PCC-CDs spray based on the results of previous experiments. Our studies demonstrate that the localized application of PCC-CDs spray precisely targets psoriatic lesions, enhancing anti-inflammatory, immunomodulatory, and skin barrier repair effects.

Methods

Preparation and Characterization of PCC-CDs, and Preparation of PCC-CDs Spray

A total of 200 grams of PCC was accurately weighed and transferred into crucibles, sealed with aluminum foil, and calcined at 400°C for 1 hour in a muffle furnace (TL0612, Beijing Zhong Ke Anbo Innovation Co., Ltd., China) to produce PCC Charcoal. The calcined material was cooled to room temperature, ground into a fine powder, and mixed with deionized water at a volume ratio of 1:20. The mixture was boiled for 2 hours, and this process was repeated three times. The resulting solutions were combined and concentrated. Subsequently, the solution underwent dialysis for 7 days using 1.0 kDa dialysis membranes, yielding a PCC-CDs solution with a final concentration of 100 mg/mL (calculated based on CDs content, Lot. No. 20240921). For every 10 mL of PCC-CDs solution, 0.2 g of PCC-CDs freeze-dried powder can be obtained, resulting in a carbon dot yield of 2%. The solution was stored at 4°C for further experiments.

The morphology, particle size distribution, and microstructure of PCC-CDs were analyzed using a transmission electron microscope (TEM, Tecnai G220; FEI Company, USA) and a high-resolution transmission electron microscope (HRTEM, JEN-1230; Japan Electron Optics Laboratory, Japan). Fluorescence properties were assessed using a spectrophotometer (F-4500, Tokyo, Japan), while surface functional groups were identified through Fourier-transform infrared (FTIR) spectroscopy (Thermo Fisher Scientific, California, USA) over a wavenumber range of 400–4000 cm−1.

An appropriate amount of stabilizer was added to the PCC-CDs solution, (An appropriate amount of glycerol was added to the PCC-CDs solution (the ratio of glycerol to the PCC-CDs solution is 1:4), mixed thoroughly, and then transferred into a spray bottle to produce the PCC-CDs spray. The concentrations for mice are 2.4 mg/d (High), 1.2 mg/d (Medium), and 0.6 mg/d (Low).

Animals and Reagents

Thirty-six Specific pathogen-free (SPF) BALB/c male mice (6–8 weeks, weighting 20.0 ± 2.0 g), were sourced from Beijing Vitalstar Biotechnology Co.,Ltd. All experimental procedures in this study were conducted in strict accordance with the requirements outlined in the AVMA Guidelines for the Euthanasia of Animals (2020 Edition) and the Guide for the Care and Use of Laboratory Animals: Eighth Edition. The study was conducted in accordance with the approval of the Experimental Animal Center of Beijing University of Chinese Medicine and the university's Ethics Committee. Approval license number: (Approval No: BUC-2024102202-4049). The present study scrupulously adheres to the ARRIVE guidelines in order to ensure transparency and reproducibility in experimental design, animal care, and euthanasia procedures. The study also complies with the core principles of the Basel Declaration and the International Council for Laboratory Animal Science (ICLAS) ethical guidelines, thus ensuring the full safeguarding of the welfare and rights of experimental animals. All experimental procedures were performed under sodium pentobarbital anesthesia, with efforts made to minimize animal suffering and reduce the number of animals used. During the experiments, animals had free access to food and water.

Imiquimod cream (IMQ) was procured from Sichuan Mingxin Pharmaceutical Co., Ltd. (Sichuan, China). Hydrocortisone butyrate cream (HBC) was purchased from Tianjin Pharmaceuticals Group Co., Ltd., (Tianjin, China). Mouse TNF-α (Cat. Ml002095M), IL-1β (Cat. Ml098416M), IL-6 (Cat. Ml098430M), IL-17A (Cat. Ml037864M), IL-22 (Cat. Ml063138M), IL-23 (Cat. Ml001919M), HMGB1 (Cat. Ml071852M), IFN-γ (Cat. Ml002277M), and VEGF (Cat. Ml002076M) ELISA kits were provided by Shanghai Enzyme-linked Biotechnology Co., Ltd. (Shanghai, China). Lipopolysaccharide (LPS) (Cat. No. L2880) was purchased from Sigma-Aldrich Trading Co., Ltd. Interferon (IFN)-γ (Cat. No. 315–05-100UG) was purchased from PeproTech Inc. RAW 264.7 (mouse monocyte-macrophage leukemia cells) (CL-0190) and RAW 264.7 cell-specific medium (CM-0190) were purchased from Procell Life Science & Technology Co., Ltd.

The following antibodies were used: PCNA antibody (Cat. 10205-2-AP, Proteintech, Wuhan, China), Ki67 Polyclonal antibody (Cat. 28074-1-AP, Proteintech, Wuhan, China), HMGB1 antibody (Cat. 10829-1-AP, Proteintech, Wuhan, China), TLR4 antibody (Cat. 30400-1-AP, Proteintech, Wuhan, China), phospho-p38 MAPK (Thr180/Tyr182) Polyclonal antibody (Cat. 28796-1-AP, Proteintech, Wuhan, China), p38 MAPK Polyclonal antibody (Cat. 14064-1-AP, Proteintech, Wuhan, China), phospho-NF-κB p65 (Ser468) Recombinant antibody (Cat. 82335-1-AP, Proteintech, Wuhan, China), NF-κB p65 Polyclonal antibody (Cat. 10745-1-AP, Proteintech, Wuhan, China), GAPDH antibody (Cat. 60004-1-Ig, Proteintech, Wuhan, China), HRP-conjugated Goat Anti-Rabbit lgG (Cat. SA00001-2, Proteintech, Wuhan, China), HRP-conjugated Goat Anti-Mouse lgG (Cat. SA00001-1, Proteintech, Wuhan, China), Pentobarbital sodium salt (Cat. P3761, Sigma-Aldrich, St. Louis, MO,USA).

Establishment of an IMQ-Induced Psoriasis Mouse Model and Drug Administration

Thirty-six BALB/c mice were randomly assigned to six groups: Control, Model, PCC-CDs spray treatment groups (High, 4.8 mg/mL; Medium, 2.4 mg/mL; Low, 1.2 mg/mL), and Positive Drug (HBC, 0.2 FTU). All experimental groups except the control received topical application of 62.5 mg of 5% imiquimod (IMQ) to the shaved dorsal area once daily at 5:00 PM for 7 consecutive days to induce psoriasis-like inflammation. Drug administration was synchronized with the initiation of IMQ-induced modeling and lasted for 7 consecutive days (from Day 1 to Day 7 of modeling). Each mouse in the high-, medium-, and low-dose PCC-CDs groups received 0.5 mL of PCC-CDs spray at the corresponding concentrations (4.8 mg/mL, 2.4 mg/mL, 1.2 mg/mL) once daily at 9:00 AM. The HBC group received 0.2 FTU of hydrocortisone butyrate cream once daily at 9:00 AM. The control group and model group received an equivalent volume of stabilizer (dissolved in deionized water) via spray once daily at 9:00 AM, while the Model group received the same stabilizer spray once daily at 9:00 AM. On the eighth day, all of the experimental mice were put on a 12-hour fast, and no water was withheld, before being sampled. The mice were then euthanized via intraperitoneal injection of sodium pentobarbital (200 mg/kg, 50 mg/mL), followed by collection of blood, spleen, and dorsal skin tissue samples for subsequent analyses. The severity of psoriasis-like skin lesions was evaluated using the Psoriasis Area and Severity Index (PASI) score, which quantifies erythema, scaling, infiltration, and thickening. Blinded assessments were independently performed by three researchers to ensure the objectivity of the results.

Histological Analysis and Immunohistochemistry Evaluation

Skin tissue samples were dehydrated through a graded series of alcohol, cleared with xylene, and embedded in paraffin. Sections (4 µm thick) were cut, deparaffinized, and stained using Hematoxylin and Eosin (H&E) or processed for immunohistochemistry. The slides were then dehydrated with anhydrous ethanol, cleared with xylene, and mounted with neutral balsam. Epidermal thickness and inflammatory infiltration were examined microscopically, while the positive areas of PCNA and Ki67 in immunohistochemistry images were quantified using Image J software.

Cell Culture and Processing

When the RAW264.7 cells reached 80% confluence, they were seeded at a density of 1×10^6 cells per well in a six-well plate. The cells were divided into the following groups: Control; Mo PCC-CDs high-concentration (PCC-CDs-H, 250 μg/mL); and PCC-CDs low-concentration (PCC-CDs-L, 125 μg/mL). All PCC-CDs concentration groups except the Control and Model groups were pretreated with the corresponding PCC-CDs solution at their respective concentrations for 3 hours. Subsequently, all groups except the blank control group were induced with 100 ng/mL LPS combined with 20 ng/mL IFN-γ for 24 hours. After induction, cell culture supernatant was collected from each group for inflammatory cytokine detection and cell lysate was collected for detection of the protein expression level.

ELISA

Inflammatory cytokine levels, including TNF-α, IL-1β, IL-6, IL-10, IL-17A, IL-22, IL-23, HMGB1, IFN-γ, and VEGF, in mouse serum or cell supernatant were measured using ELISA according to the manufacturer's instructions.

Western Blotting

Proteins (20 µg) were extracted from the samples using 200 µL of RIPA buffer and adjusted to equal concentrations with a BCA kit. The denatured proteins were separated by gel electrophoresis and transferred onto PVDF membranes. The membranes were incubated overnight at 4°C with specific primary antibodies, followed by a 1-hour incubation at room temperature with HRP-conjugated anti-rabbit secondary antibodies. Protein bands were visualized and quantified using Image Lab software, and their relative expression levels were normalized to GAPDH.

Transcriptomics Analysis

Total RNA was extracted with TRIzol® Reagent. Paired-end libraries were prepared using the TruSeq™ RNA Sample Preparation Kit, involving mRNA isolation, fragmentation, and reverse transcription into cDNA. This was followed by end-repair, "A" base addition, and PCR enrichment. The library was validated using a Qubit® 2.0 Fluorometer and an Agilent 2100 Bioanalyzer, then sequenced on the NovaSeq6000 platform. Differential expression analysis, conducted with edgeR, identified significant genes ($P < 0.05$, $|\log2$ Fold Change (FC)$| \geq 1$). KEGG and GO enrichment analyses were performed to understand significant genes' functional roles, with significant pathways visualized in DAVID.

Statistical Analysis

Data are presented as mean ± standard deviation (SD). Analyses were conducted using GraphPad Prism 10.0 software. Statistical significance was assessed using one-way analysis of variance (ANOVA) and multifactorial ANOVA, followed by multiple comparisons with Dunn's post hoc test. A p-value of less than 0.05 was considered statistically significant.

Results

Characterization of PCC-CDs

TEM and HRTEM reveal that PCC-CDs are nearly spherical nanoparticles, uniformly dispersed in an aqueous medium with sizes ranging from 1.05 to 3.48 nm (average 2.18 ± 0.45 nm), exhibiting a well-defined lattice structure with a 0.223 nm spacing. The conspicuous Tyndall effect in the PCC-CDs solution is visible (Figure 1A–C). Additionally, the zeta potential of PCC-CDs is approximately −10 mV, indicating a negatively charged surface, which suggests low toxicity (Figure 1D). X-ray diffraction (XRD) confirms the crystalline/amorphous carbon structure, with a pronounced peak at $2\theta = 28.76°$, corresponding to a lattice spacing of 0.16 nm (Figure 1E). The UV spectrum of PCC-CDs indicates π–π* and n–π* electronic transitions near 270 nm and 340 nm, respectively, which are associated with surface states such as C=C, C=O, C=N, and C–O (Figure 1F). Fluorescence spectra show that the excitation peak (EX_{max}) and emission peak (EM_{max}) of PCC-CDs solution are at 370 nm and 467 nm, respectively (Figure 1G). PCC-CDs solution was qualitatively analyzed using FTIR and X-ray photoelectron spectroscopy (XPS). As shown in Figure 1H, the infrared results exhibit a series of characteristic peaks at 3418 cm-1, 2965 cm-1, 1568 cm-1, 1309 cm-1, and 1046 cm-1, corresponding to the stretching vibrations of O/N-H, C-H, C=O, C-N, and C-O, respectively. Similarly, XPS results indicate that PCC-CDs solution are primarily composed of C, N, and O elements, with proportions of 70.85%, 4%, and 25.15%, respectively. Three distinct peaks were observed at 284.6 eV, 399.63 eV, and 531.71 eV, corresponding to C 1s, N 1s, and O 1s. The C 1s spectrum can be deconvoluted into three peaks at 284.80 eV (C=C/C-C), 284.2 eV (C-O), and 286.5 eV (C=O/C=N). The O 1s and N 1s spectra can each be deconvoluted into two peaks at 531.7 eV (C-O) and 533.2 eV (C=O), and at 399.4 eV (N-H) and 400.1 eV (C-N), respectively. These findings indicate that PCC-CDs predominantly contain active groups such as hydroxyl, carboxyl, and amino groups (Figure 1I–L).

PCC-CDs Spray Markedly Mitigate IMQ-Induced Psoriasiform Dermatitis in Mice

To further investigate the efficiency and mechanism by which PCC-CDs spray ameliorates psoriasis in mice, we applied IMQ cream to the dorsal skin of BALB/c mice for seven consecutive days to establish a psoriasis-like dermatitis model. Following IMQ induction, the PCC-CDs and HBC groups received their respective treatments (Figure 2A). In comparison to the control group, the IMQ-induced psoriasis mice exhibited pronounced erythema, scaling, and thickening of the skin. Notably, the lesions in the PCC-CDs and HBC treatment groups showed significant improvement, (Figure 2B).

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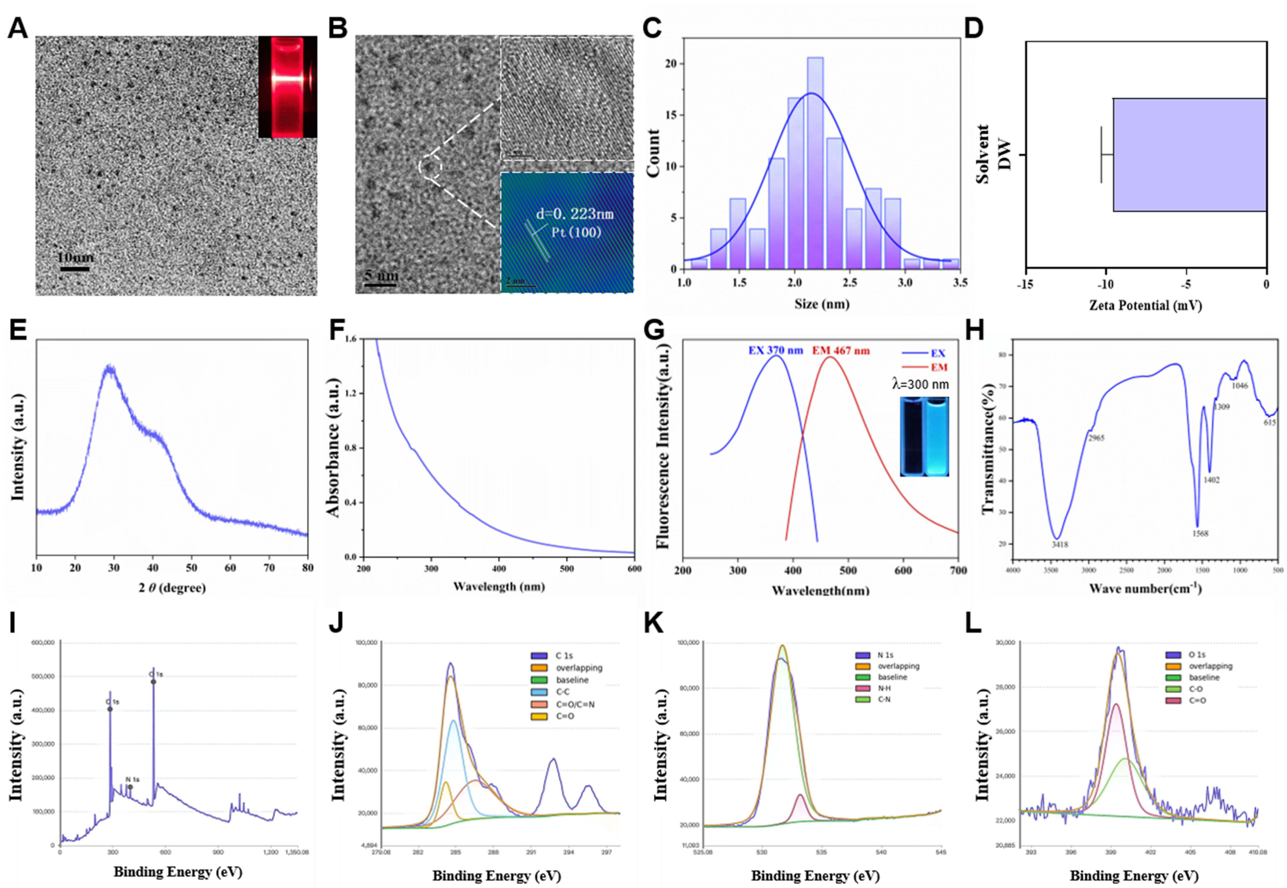

Figure 1 Characterization of PCC-CDs solution. (**A**) Transmission electron microscopy (TEM) images and the Tyndall effect of PCC-CDs. (**B**) High-resolution TEM (HRTEM) image of PCC-CDs and the lattice spacing of PCC-CDs. (**C**)The particle size distribution histogram of PCC-CDs. (**D**) The zeta potential of PCC-CDs solution in DW. (**E**) X-ray diffraction pattern of PCC-CDs. (**F**) UV-visible spectrum of PCC-CDs. (**G**) Fluorescence spectra for excitation and emission. (**H**) Fourier transform infra-red spectrum. (**I**) X-ray photoelectron spectroscopy survey of PCC-CDs. (**J**) C1s. (**K**) O1s and (**L**) N1s.

These observations were quantified using the Psoriasis Area and Severity Index (PASI) score. As shown in Figure 2C, compared with the control group, PASI scores for erythema, scaling, and thickening in IMQ-induced psoriasis mice significantly increased by day 3 of modeling. Following intervention with different doses of PCC-CDs, all PASI scores significantly decreased in a dose-dependent manner. The efficacy of high-dose PCC-CDs was approximately equivalent to that of HBC. Additionally, after treatment with IMQ, mice in all groups experienced gradual weight loss and a notable increase in spleen index. However, the HBC group demonstrated a steady weight gain starting on the third day of treatment, while the PCC-CDs groups exhibited significant weight gain from the fourth day, along with a marked decrease in spleen index. And the spleen morphology clearly demonstrates differences in size, color, and texture among groups: compared with the normal control group, the spleen in the psoriasis model group exhibited obvious enlargement and darkening of color. Following PCC-CDs and HBC intervention, spleen morphology was significantly restored with reduced volume (Figure 2D and E). Thus, PCC-CDs spray effectively ameliorate IMQ-induced psoriasis-like dermatitis and reverse the changes in body weight and spleen index.

PCC-CDs Spray Significantly Alleviate Inflammatory Responses in IMQ-Induced Psoriasis in Mice

Histopathological analysis revealed that the skin structure of mice in the control group was normal, exhibiting no evident hyperkeratosis in the epidermis and no inflammatory cell infiltration in the dermis. In contrast, the skin tissues of IMQ-induced psoriatic mice exhibited severe pathological damage and disorganized structure: irregular thickening and

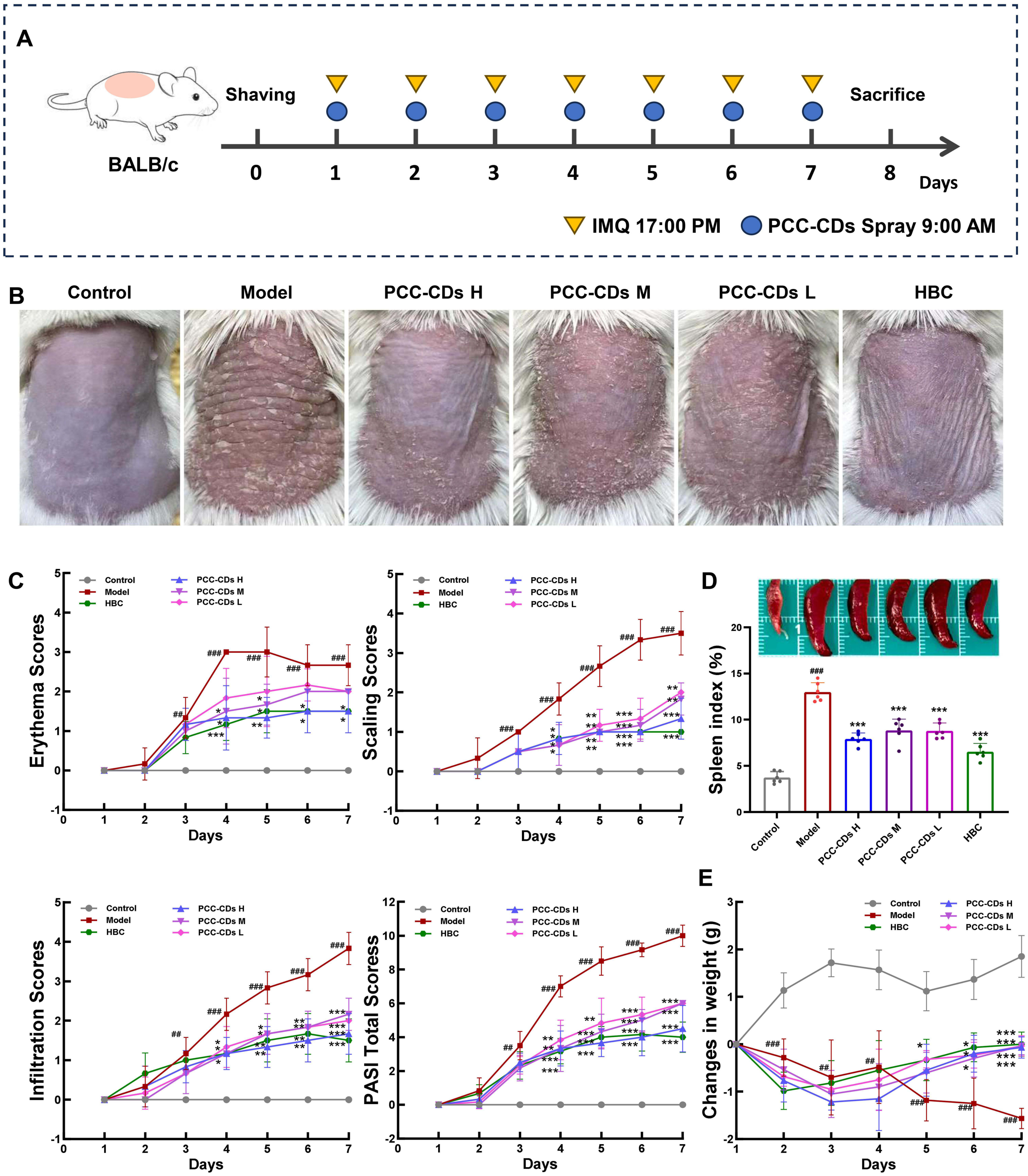

Figure 2 PCC-CDs spray improve IMQ-induced psoriasis-like dermatitis in mice. (**A**) Protocol for the efficacy of PCC-CDs on the IMQ-induced psoriasis mouse model. (**B**) Appearance of the back skin tissue of IMQ-induced psoriasis-like mice on the seventh day after PCC-CDs treatment. (**C**) PASI score (erythema, scaling, infiltration and total score). (**D**) Body weight change. (**E**) Spleen index. Each group n = 6. Data were expressed as means ± standard deviation (SD). ##P < 0.01, ###P < 0.001 vs Control group; **P < 0.01, ***P < 0.001 vs Model group.

shedding of the stratum corneum, thickening of the spinous layer, and dermal capillary dilation along with substantial inflammatory cell infiltration. Treatment with PCC-CDs spray and HBC significantly improved cellular infiltration and pathological changes (Figure 3A). PCNA and Ki67 are critical markers of cell proliferation, with existing studies indicating a positive correlation between their levels in psoriatic lesions and PASI scores. Immunohistochemical analysis

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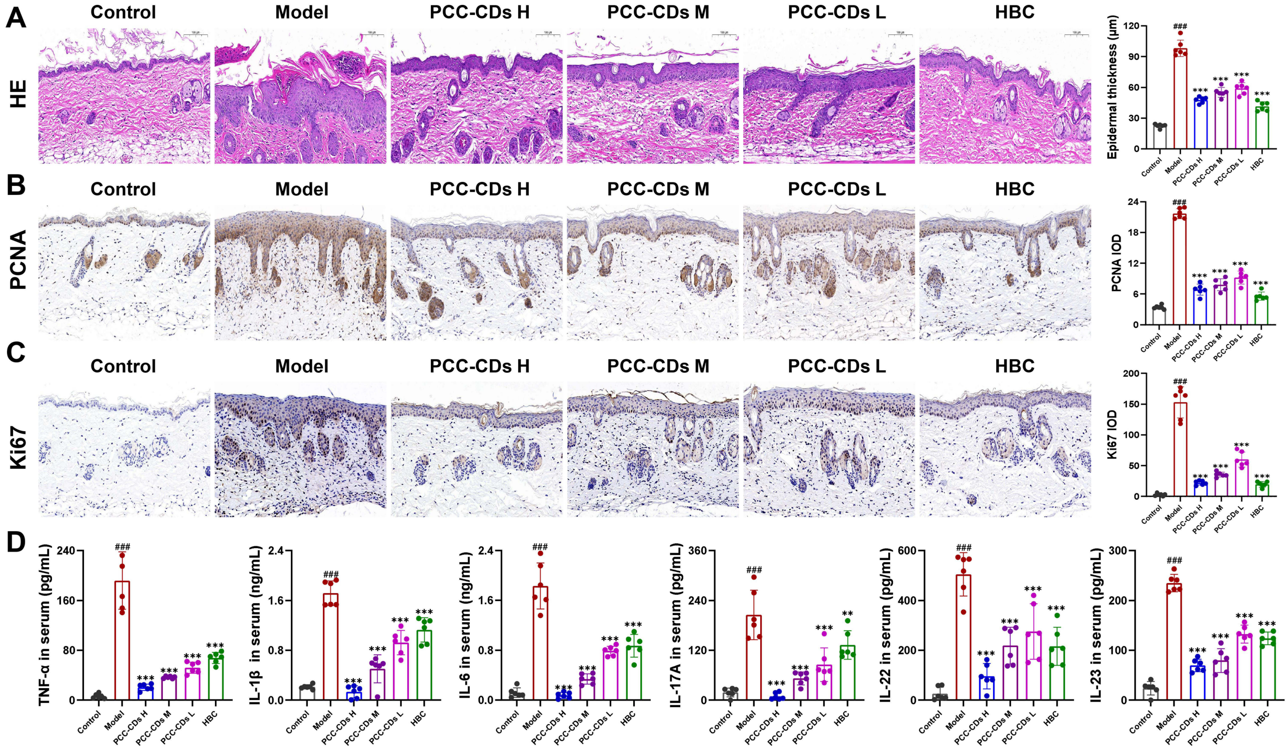

Figure 3 PCC-CDs spray reduced IMQ-mediated inflammatory response. (**A**) HE staining of the back skin tissue of IMQ-induced psoriasis-like mice and the changes of Epidermal thickness (200×). Expression of (**B**) PCNA and (**C**) Ki67 (200×) and the integral optical density (IDO) of PCNA and Ki67 using immunohistochemistry. (**D**) Serum levels of TNF-α, IL-1β, IL-6, IL-17A, IL-22, and IL-23 in mice. Each group n = 6. Data were expressed as means ± standard deviation (SD). $^{###}P < 0.001$ vs Control group; $^{**}P < 0.01$, $^{***}P < 0.001$vs Model group.

showed high expression levels of PCNA and Ki67 in the epidermis of model mice, which were significantly reduced following treatment with PCC-CDs or HBC. PCC-CDs demonstrated superior efficacy over HBC (Figure 3B and C). To clarify the systemic inflammatory status in IMQ-induced model mice, ELISA was employed to detect serum levels of key inflammatory mediators. The results showed a significant elevation in the concentrations of TNF-α, IL-1β, IL-6, IL-17A, IL-22, and IL-23 in the model group compared with the normal control group. This elevation is biologically meaningful: TNF-α, as a central proinflammatory cytokine, mediates the activation of downstream inflammatory cascades and promotes tissue damage; IL-1β initiates the early-stage inflammatory response by inducing endothelial cell activation and leukocyte recruitment; IL-6 regulates the acute-phase reaction and enhances the survival of proinflammatory cells; while IL-17A, IL-22, and IL-23—key cytokines of the Th17 cell axis—synergistically promote keratinocyte hyperproliferation and neutrophil infiltration, which are core features of IMQ-induced inflammatory pathology. Collectively, these elevated cytokine levels confirm that IMQ successfully induces a multi-dimensional systemic inflammatory response in mice. Subsequently, to evaluate the anti-inflammatory effect of PCC-CDs, the model mice were treated with PCC-CDs at high, medium, and low concentrations. ELISA detection revealed that PCC-CDs treatment markedly reduced the serum levels of the aforementioned six inflammatory cytokines, and this inhibitory effect exhibited a clear concentration-dependent trend, further confirming the dose-dependent anti-inflammatory activity of PCC-CDs (Figure 3D). In summary, these findings demonstrate that the treatment of PCC-CDs spray improves erythema, scaling, and thickness in IMQ-induced psoriatic mice, while also mitigating inflammatory responses and inhibiting cell proliferation.

Transcriptomic Analysis Investigates the Potential Mechanisms by Which PCC-CDs Spray Ameliorates Psoriasis in Mice

To investigate the potential mechanisms by which PCC-CDs spray inhibit the inflammatory processes associated with psoriasis, we conducted a transcriptomic analysis of the dorsal skin of mice. Utilizing a criterion of $P < 0.05$ and

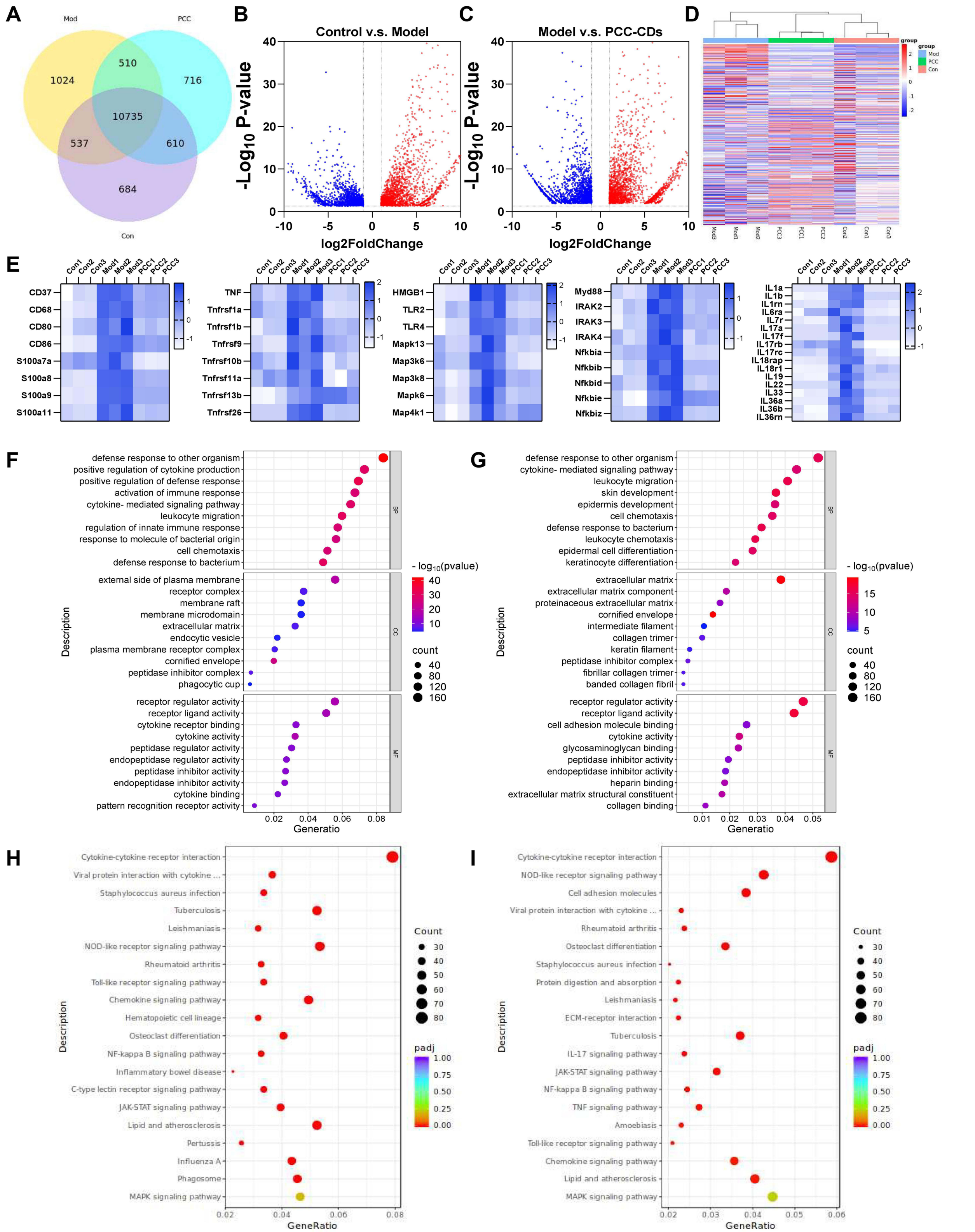

Figure 4 Transcriptomic analysis of PCC-CDs spray regulating psoriasis. (**A**) Venn diagram showing the intersection of differentially expressed genes (DEGs) among the control group, model group, and PCC-CDs group. (**B**) Volcano map of DEGs between the Control and Model group. (**C**) Volcano map of DEGs between the Model and PCC-CDs group. (**D**) Heatmap of the DEGs among the control, model, and PCC-CDs group. (**E**) Heatmap of core genes regulated by PCC-CDs. (**F**) Enrichment analysis of KEGG for DEGs between the Control and Model group. (**G**) Enrichment analysis of KEGG for DEGs between the Model and PCC-CDs group. (**H**) Biological process analysis, Cellular component analysis, and Molecular function analysis of the DEGs between the Control and Model group. (**I**) Biological process analysis, Cellular component analysis, and Molecular function analysis of the DEGs between the Model and PCC-CDs group.

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|Log2FoldChange(FC)|≥1, we analyzed the transcriptomic data to identify differentially expressed genes (DEGs). A Venn diagram illustrated the intersection of DEGs among the *Control group, Model group*, and *PCC-CDs treatment group* (Figure 4A). The volcano plot indicated that the DEGs identified between the *Control group* versus *Model group* and *Model group* versus *PCC-CDs treatment group* may represent crucial genes involved in the amelioration of psoriasis-like skin inflammation by PCC-CDs (Figure 4B and C). The specific DEGs associated with the reversal of psoriasis-like inflammation by PCC-CDs are illustrated in Figure 4D. In comparison to the control group, the model group exhibited a substantial increase in cell phenotypes associated with the innate immune response, including CD14, CD37, CD68, CD86, and CD163, alongside an elevation in various inflammatory mediators. This observation indicates that the inflammatory response associated with psoriasis involves the activation of dendritic cells, monocytes, macrophages, T cells, and B cells. Furthermore, the key genes, particularly HMGB1, as well as the cell membrane receptor TLR4 and its downstream signaling pathways, including MAPK and NF-κB, were significantly overexpressed in the model group. In contrast, PCC-CDs effectively reversed the expression of these essential DEGs (Figure 4E). Additionally, utilizing the DAVID bioinformatics tool, we respectively performed KEGG and GO enrichment analyses on the DEGs derived from comparisons between the *Control group* versus *Model group* and *Model group* versus *PCC-CDs treatment group* (Figure 4F–I). The results indicated that PCC-CDs spray inhibited excessive keratinization and the immune response in psoriatic epidermal cells. The psoriasis-related signaling pathways primarily involved IL-17, TNF, MAPK, NF-κB, JAK-STAT, and Toll-like receptor pathways. These findings suggest that PCC-CDs spray may ameliorate psoriasis through the inhibition of the HMGB1/TLR4/MAPK/NF-κB signaling pathways.

PCC-CDs Spray Modulate the HMGB1/MAPK/NF-κB Signaling Pathway to Alleviate Psoriasis-Like Mice

To further verify whether PCC-CDs spray exert their anti-psoriatic effects by modulating HMGB1 and influencing key targets in downstream signaling pathways such as MAPK, NF-κB, and JAK/STAT, we employed ELISA and Western blot analyses to assess protein levels in the serum and skin tissues of mice from different groups. Figure 5A illustrates that the levels of inflammatory cytokines IFN-γ, HMGB1, and the pro-angiogenic factor VEGF were significantly elevated in the serum of IMQ-induced mice compared to the control group. Treatment with PCC-CDs spray resulted in a marked, concentration-dependent reduction in these cytokine levels. Western blot results demonstrated a significant increase in HMGB1 protein expression in the skin tissues of the model group compared to the control group, along with activation of the membrane receptor protein TLR4, which subsequently enhanced the phosphorylation levels of MAPK p38 and NF-κB p65. Conversely, the PCC-CDs treatment group exhibited a significant reduction in the protein levels of HMGB1 and TLR4, as well as inhibition of MAPK p38 and NF-κB p65 phosphorylation (Figure 5B). These findings confirm that PCC-CDs spray can ameliorate the inflammatory response in IMQ-mediated psoriatic mice by inhibiting the HMGB1/MAPK/NF-κB pathway.

PCC-CDs Inhibit M1 Polarization of Macrophages by Suppressing the HMGB1/TLR4/MyD88/NF-κB Pathway

To confirm this, we selected Raw264.7 macrophages and used an in vitro model of LPS- and IFN-γ-induced M1 polarization. ELISA and Western blot analyses were employed to assess the levels of relevant factors in the cell supernatant and the expression of target proteins within the cells. Figure 6A shows that, compared to the control group, the levels of the inflammatory cytokines HMGB1, TNF-α, IL-1β and IL-6 in the LPS+IFN-γ-induced Raw264.7 macrophage cell supernatant were significantly higher, while the level of the anti-inflammatory factor IL-10 was significantly lower. Treatment with PCC-CDs (at concentrations of 125 μg/mL and 250 μg/mL) resulted in a significant, concentration-dependent reduction in the levels of the aforementioned pro-inflammatory cytokines. This was accompanied by a notable increase in the level of the anti-inflammatory factor IL-10. The high concentration PCC-CDs group exhibited a more pronounced regulatory effect than the low concentration group.

Western blot analysis demonstrated that, compared to the control group, RAW264.7 macrophages induced by LPS +IFN-γ exhibited significantly higher levels of HMGB1, TLR4, MyD88 and phosphorylated NF-κB p65 protein

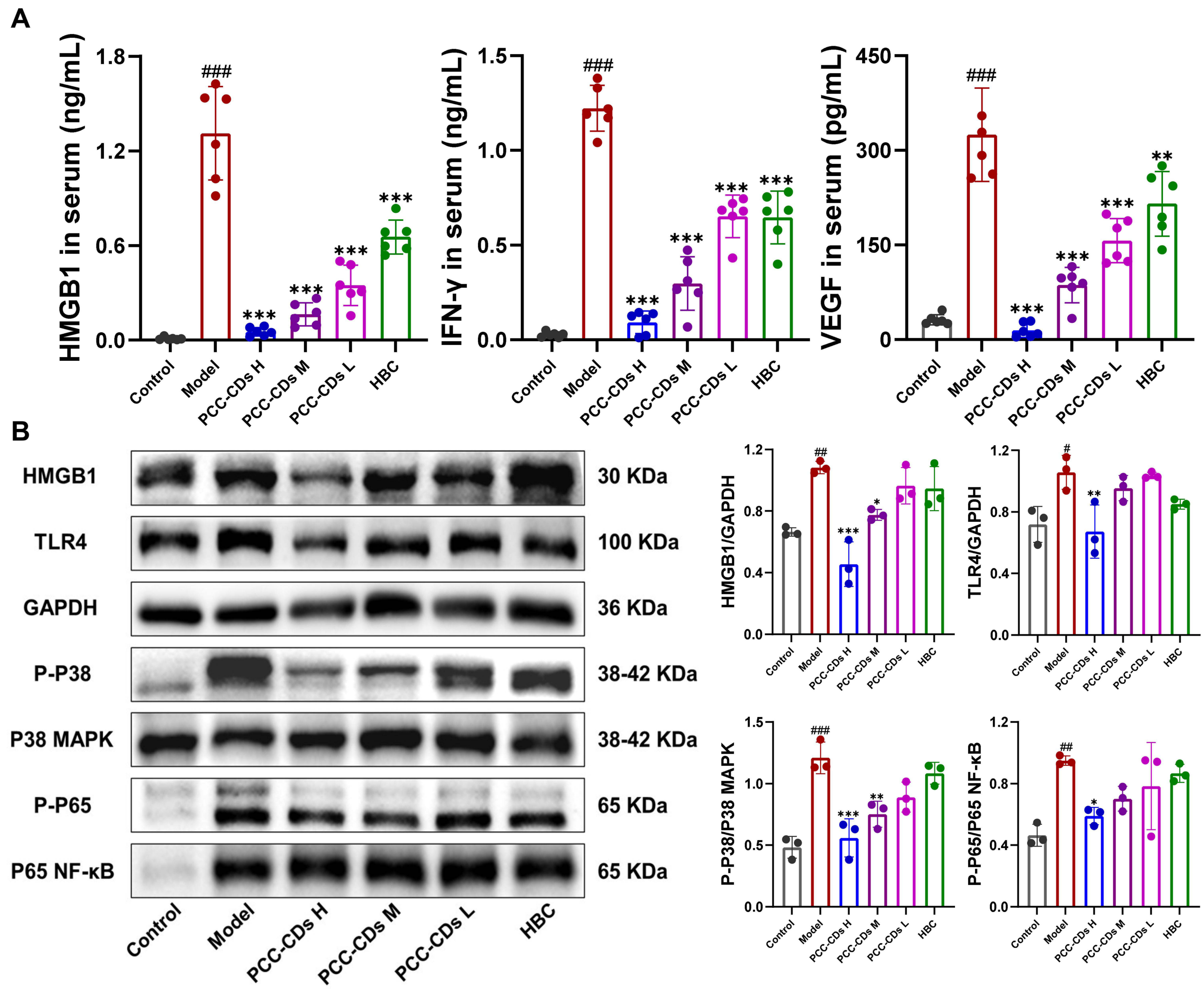

Figure 5 PCC-CDs spray regulate the HMGB1/TLR4/MAPK/NF-κB signaling pathway to ameliorate psoriasis-like dermatitis. (**A**) Serum levels of HMGB1, IFN-γ, and VEGF in mice. (**B**) Protein expression levels of HMGB1/TLR4/MAPK/NF-κB signaling pathway-related proteins in mouse skin tissues. Each group n = 3. Data were expressed as means ± standard deviation (SD). $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ vs Control group; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$vs Model group.

expression. This indicates that the HMGB1/TLR4/MyD88/NF-κB signaling pathway is significantly activated in M1-polarised macrophages. Conversely, both the low- and high-concentration PCC-CDs treatment groups exhibited a significant reduction in HMGB1, TLR4 and MyD88 protein levels, as well as obvious inhibition of NF-κB p65 phosphorylation. This regulatory effect was concentration-dependent: the high-concentration PCC-CDs group showed a stronger inhibitory effect than the low-concentration group (Figure 6B). These findings confirm that PCC-CDs can inhibit the polarization of Raw264.7 macrophages towards the M1 phenotype induced by LPS combined with IFN-γ, thereby exerting anti-inflammatory effects related to psoriasis improvement, by suppressing the HMGB1/TLR4/MyD88/NF-κB pathway in a concentration-dependent manner.

Discussion

Psoriasis is a chronic inflammatory skin disease that is mediated by the immune system, marked by the hyperproliferation and aberrant differentiation of keratinocytes, which results in the formation of well-demarcated scales on the skin's surface.[32] The condition is associated with a high recurrence rate, presents significant challenges in terms of cure, and profoundly compromises the quality of life for patients.[33] Currently, the primary therapeutic agents employed for psoriasis are methotrexate, corticosteroids, and immunosuppressive drugs.[34–36] Notably, corticosteroids can significantly

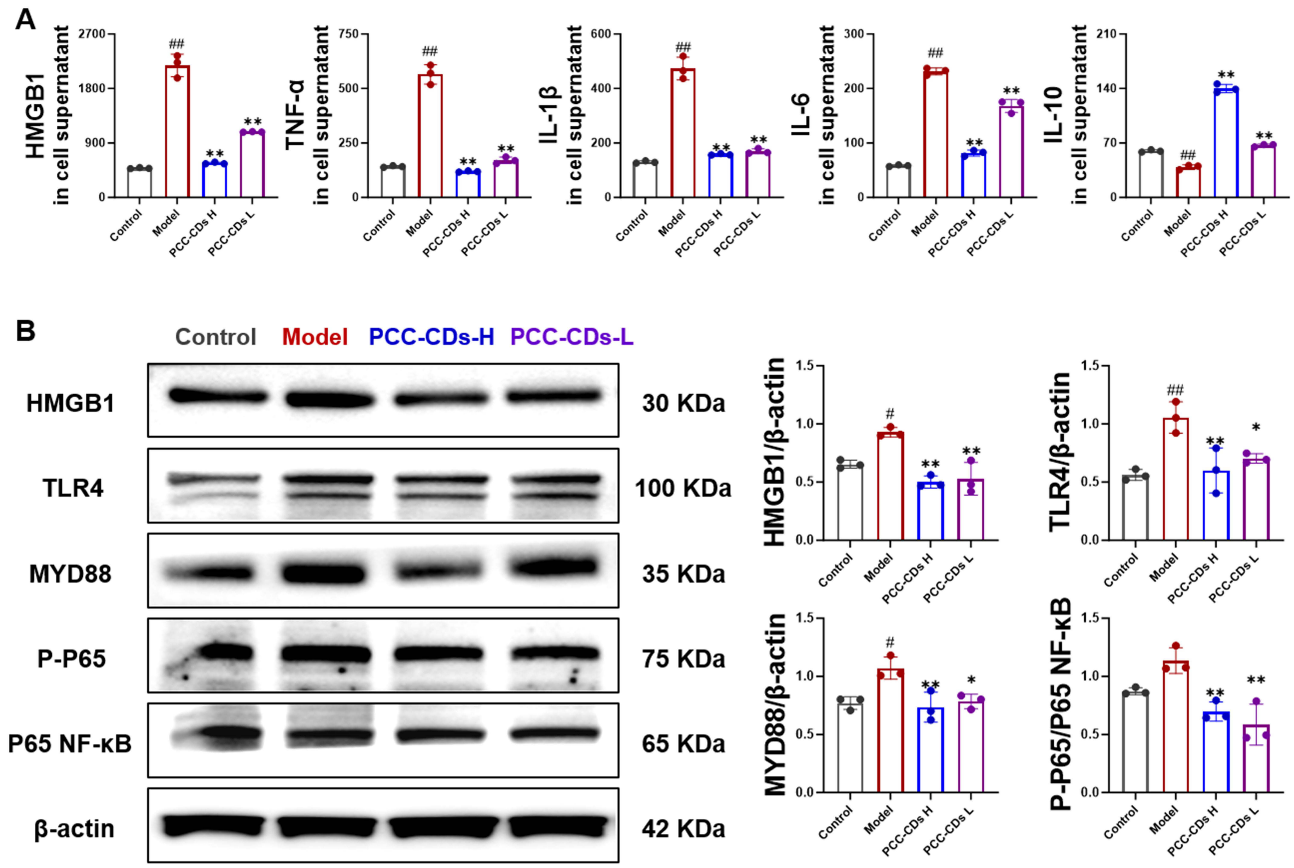

Figure 6 PCC-CDs alleviate M1 macrophage polarisation by modulating the HMGB1/TLR4/NF-κB signalling pathway. (**A**) Cytokine levels in cell supernatants, including HMGB1, TNF-α, IL-1β, IL-6 and IL-10. (**B**) The effects of PCC-CD intervention on HMGB1/TLR4/NF-κB protein expression in M1 macrophages (n = 3 per group). Data are expressed as mean ± standard deviation (SD). $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ compared with the control group; $^{*}P < 0.05$, $^{**}P < 0.01$ compared with the model group.

suppress inflammatory responses in the skin and relieve pruritic symptoms; however, their use is frequently associated with various adverse effects, including allergic reactions and gastrointestinal disturbances. Prolonged usage may result in severe complications, including aplastic anemia and liver dysfunction.[37,38] Furthermore, while immunosuppressive agents effectively address key pathological mechanisms of psoriasis, particularly those involving the immune response mediated by the IL-23/Th17 axis, and demonstrate considerable clinical efficacy, biologics encounter numerous challenges owing to the induction of immune responses that may result in treatment resistance, reduced efficacy, and various side effects.[39–41] Consequently, there is an urgent necessity to explore innovative and effective therapeutic strategies.

HMGB1 serves as a critical inflammatory mediator, and its role in peripheral inflammatory and autoimmune disorders is of particular relevance to psoriasis. Its pro-inflammatory activities are primarily exerted through interactions with toll-like receptors (TLRs) and the receptor for advanced glycation end products (RAGE), which trigger downstream pro-inflammatory signaling cascades.[42–44] Specifically, HMGB1 modulates the activation of inflammatory cells involved in psoriasis pathogenesis and promotes the secretion of pro-inflammatory cytokines via pathways such as RAGE/cathepsin B and TLR4/NF-κB.[45,46] As a key driver of systemic inflammation and autoimmune responses, HMGB1 is also recognized as a promising therapeutic target, and this pro-inflammatory property is closely consistent with its pathogenic role in psoriasis.[47,48]

The primary pathological mechanisms of psoriasis are closely associated with the dysfunction of psoriatic epidermal immune cells and the subsequent excessive inflammatory response.[49,50] It has been demonstrated by numerous studies that the expression of HMGB1 is significantly increased in the cytoplasm of epidermal cells in psoriatic lesions and in the serum of psoriasis patients,[51,52] and its expression level is positively correlated with the severity of the diseases.[53] In psoriatic lesional skin, HMGB1 is secreted by keratinocytes and various immune cells, including activated macrophages, mature dendritic cells, and natural killer cells.[54,55] Furthermore, by binding to receptors such as RAGE and TLR4, HMGB1 has been demonstrated to induce the release of multiple pro-inflammatory mediators.[56,57] This established inflammatory microenvironment further promotes HMGB1 secretion from keratinocytes, forming a positive feedback loop that aggravates skin inflammation.[58] Consequently, the strategic delivery of HMGB1 has emerged as a promising avenue for modulating immune responses and mitigating inflammatory responses in affected regions.[59]

In view of this intricate pathological process, traditional Chinese medicine (TCM) -derived active components have long been recognized for their inherent anti-inflammatory potential in psoriasis treatment.[60] However, their clinical translation is often hampered by inherent limitations such as poor water solubility, low bioavailability, and inadequate targeted delivery to lesion sites.[61,62] It is noteworthy that the integration of contemporary nanotechnology, particularly carrier-free nano systems, has emerged as a transformative strategy to address these bottlenecks. The core value of this approach is to amplify the anti-inflammatory efficacy of TCM components by optimizing their delivery efficiency and biological activity.[63–65] Keshari et al reported that soya lecithin-PLGA hybrid nanocomposites, tailored for resveratrol delivery, enhanced skin penetration, retention, and adhesive properties in psoriatic lesions, thereby exerting significant anti-psoriatic efficacy alongside excellent safety and biocompatibility.[66] Similarly, Zhang et al reported a carrier-free nano-Tetrandrine, which significantly reduced epidermal inflammation in imiquimod-induced psoriasis through GSDMC-dependent non-inflammatory thermo-apoptosis-mediated anti-psoriatic effects.[67]

In our study, PCC-CDs, a novel drug delivery system that synergizes TCM with contemporary nanotechnology, have increasingly attracted significant attention within the medical community due to their unique, prolonged anti-inflammatory effects and remarkable bioavailability. Prior studies have shown that the intraperitoneal administration of PCC-CDs significantly inhibits M1 polarization of macrophages and alleviates epidermal inflammation in IMQ-induced psoriasis-like murine models. Nonetheless, the pharmacological mechanisms underpinning the anti-psoriatic efficacy of topical PCC-CDs spray remain to be elucidated. Consequently, the present study systematically explores the mechanisms of PCC-CDs spray in treating psoriasis through pharmacological studies in vivo and in vitro experiments.

PCC has been historically utilized in China for various applications. Previous studies by our research group demonstrated that the carbon dots exhibit significant anti-psoriasis effects, and we optimized their preparation process. In this study, we synthesized the PCC-CDs using the optimized process and formulated them into an easy-to-use topical spray. In clinal, we observed that the topical application of PCC-CDs spray significantly alleviated erythema, scaling, and epidermal thickening at the affected sites in psoriasis patients, along with a substantial reduction in subjective pruritus. In the IMQ-induced psoriasis mouse model, body weight diminished, the spleen index increased, and the PASI scores for erythema, scaling, and thickening progressively elevated over time. Histopathological analysis demonstrated pronounced epidermal thickening accompanied by substantial infiltration of inflammatory cells within the subcutaneous tissue of model mice, as well as a significant increase in the protein expression of PCNA and Ki67. ELISA results indicated that levels of inflammatory cytokines, including TNF-α, IL-1β, IL-6, IL-17A, IL-22, and IL-23, were markedly elevated in the serum of mice post-IMQ induction. Conversely, treatment with PCC-CDs spray at varying doses led to an increase in body weight, a significant reduction in epidermal thickness and PASI scores, amelioration of histopathological damage, and a decrease in the levels of PCNA, Ki67, and inflammatory cytokines in psoriasis mice, in a dose-dependent manner.

Given the ambiguous pharmacological mechanisms of PCC-CDs spray, this study first utilized transcriptomic technology to systematically elucidate the potential pharmacological pathways associated with PCC-CDs spray in the treatment of psoriasis-like dermatitis. Transcriptomic analysis results indicated that PCC-CDs spray may exert a therapeutic effect by downregulating multiple immune and inflammation-related signaling cascades, specifically including TNF, Toll-like receptors, NF-κB, MAPK, and JAK/STATs signaling pathway. Furthermore, to further verify the above transcriptomic findings and clarify the key regulatory targets, in vitro experiments were performed using RAW264.7 macrophages. Specifically, RAW264.7 macrophages were induced to polarize into M1 phenotype by LPS and IFN-γ. The results showed that M1-polarized macrophages actively secreted large amounts of HMGB1 and pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6. Meanwhile, the protein expression level of HMGB1 in M1 macrophages was significantly upregulated, which further activated the phosphorylation of downstream TLR4/MyD88/NF-κB signaling pathway, thereby amplifying the inflammatory response cascade. Notably, treatment with PCC-CDs could effectively inhibit the expression of HMGB1 in M1 macrophages, and this inhibitory effect further led to the suppression of the phosphorylation levels of the downstream inflammatory pathways. Moreover, in order to validate the

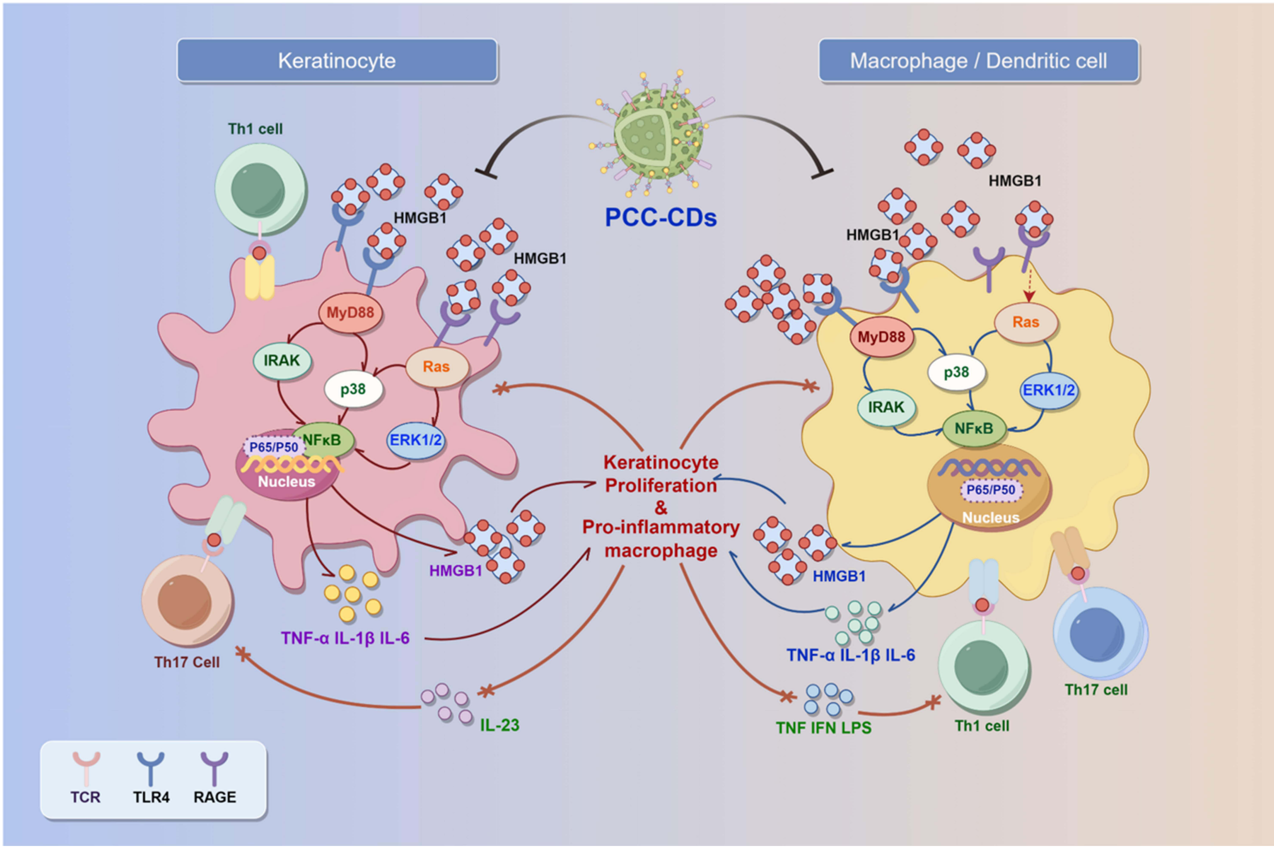

Figure 7 Schematic illustration of the therapeutic mechanism hypothesis of PCC-CDs spray in alleviating psoriatic inflammation via modulation of the HMGB1/TLR4/MAPK/NF-κB signaling pathway.

regulatory effect of PCC-CDs spray on the aforementioned inflammatory response process in vivo, Western blot analyses were conducted on mouse skin tissue proteins. The results demonstrated that HMGB1 could significantly amplify the immune response of epidermal cells by binding to TLR4 receptor and activating MAPK and NF-κB signaling pathways. In contrast, PCC-CDs spray has been shown to modulate the functional activity of HMGB1, with a significant suppression of the phosphorylation levels of MAPK and NF-κB signaling pathways associated with inflammation in mouse skin tissues. This results in the blocking of the amplification of the inflammatory response cascade, thereby exerting a therapeutic effect on psoriasis-like dermatitis (Figure 7).

Conclusion

PCC-CDs spray effectively ameliorates the characteristic pathological manifestations of IMQ-induced psoriasis in mice, including weight loss, reduced PASI scores, elevated pro-inflammatory cytokine levels, and histopathological damage. Mechanistically, PCC-CDs exerts its therapeutic effect by inhibiting the protein expression of the HMGB1/TLR4/MAPK/NF-κB pathway, thereby improving IMQ-induced psoriasis-like inflammatory responses. This distinctive inhibitory mechanism offers a novel potential therapeutic strategy for the management of psoriasis in clinical settings. The present study is subject to certain limitations, including its exclusive focus on animal and cell experiments. In order to validate the clinical applicability of PCC-CDs, further clinical research is required that recruits human subjects. Subsequent studies should be performed to co-culture keratinocytes and immune cells in order to explore the specific molecular targets of PCC-CDs in regulating the HMGB1/TLR4/MAPK/NF-κB pathway.

Abbreviations

CDs, Carbon dots; FTIR, Fourier-transform infrared; H&E, Hematoxylin and Eosin; HRTEM, High-resolution transmission electron microscope; HBC, Hydrocortisone butyrate cream; IMQ, Imiquimod; IHC, Immunohistochemistry; PCC, Phellodendri Chinensis Cortex; PASI, Psoriasis Area and Severity Index; RAGE, Receptor for advanced glycation end-products; SPF, specific pathogen-free; TLR, Toll-like receptorTEM, Transmission electron microscope; TCM, Traditional Chinese medicine.

Data Sharing Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

Ethics Statement

The animal study was approved by the Ethics Committee of Beijing University of Chinese Medicine (Approval No: BUC-2024102202-4049).

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Disclosure

The authors assert that this research was conducted in the absence of any commercial or financial relationships that might be construed as a potential conflict of interest.

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