

Multitarget aminated fullerene hydrogels ameliorate psoriasis by scavenging ROS, inhibiting keratinocyte hyperproliferation, and reshaping the inflammatory microenvironment

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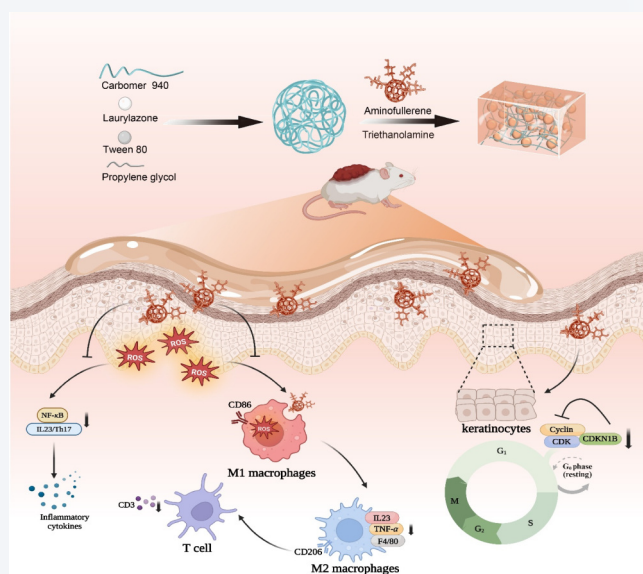
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ABSTRACT: Psoriasis is a chronic inflammatory skin disease driven by oxidative stress, keratinocyte hyperproliferation, and immune dysregulation. Conventional single-target therapies frequently result in incomplete remission and disease relapse. Here, we designed amino-functionalized fullerene hydrogels (TAPC@CB/TPPC@CB) that coordinately restore oxidative and inflammatory homeostasis via a multitarget mechanism. These hydrogels normalize keratinocyte proliferation by upregulating the cell-cycle inhibitor Cdkn1b, inducing G0/G1 arrest, and eliminating excessive reactive oxygen species (ROS). They also promote macrophage polarization toward the anti-inflammatory M2 phenotype and downregulate stress-related and proinflammatory proteins, thereby inhibiting the NF- κ B/IL-23/Th17 axis and restoring the inflammatory microenvironment. *In vivo*, topical TAPC@CB significantly reduced macrophage and T-cell infiltration, alleviated inflammation, and lowered recurrence risk. This study establishes amino-fullerene-based hydrogels as a single-agent, multipathway nanotherapeutic strategy for effective psoriasis treatment and relapse prevention.

KEYWORDS: fullerene, psoriasis, reactive oxygen species (ROS), inflammation, keratinocyte hyperproliferation, multitarget mechanism, relapse



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1 Introduction

Psoriasis is a chronic inflammatory skin disease characterized by keratinocyte hyperproliferation, immune dysregulation, and well-defined clinical features including erythema, scaling, and epidermal thickening [1, 2]. It affects 2%–3% of the global population, with a

recurrence rate as high as 90%, significantly impairing patients' quality of life [3, 4]. Elevated levels of reactive oxygen species (ROS) are recognized as an upstream driver in psoriasis pathogenesis, promoting nuclear factor- κ B (NF- κ B) activation and subsequent release of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-23 (IL-23), and interleukin 17 (IL-17) [5–8]. These cytokines create a self-amplifying inflammatory microenvironment that perpetuates keratinocyte proliferation and immune cell infiltration [9, 10]. Moreover, oxidative stress and chronic inflammation facilitate the formation of tissue-resident memory T (TRM) cells, which can rapidly reignite localized inflammation upon re-exposure to triggers, leading to disease recurrence [11–13].

Topical agents remain a cornerstone of psoriasis management, primarily aiming to inhibit keratinocyte proliferation [14], reduce inflammation [15], and modulate immune responses [16]. Although biologics targeting single cytokines (e.g., TNF- α , IL-17) offer high specificity, they often fail to address the multifactorial nature of psoriasis, resulting in incomplete responses or relapse [17]. While combination therapies can cover multiple pathways, they raise concerns regarding stability, compatibility, and cumulative side effects [18]. Consequently, developing single agents capable of simultaneously quenching ROS, suppressing pathological keratinocyte growth, and controlling inflammation represents a promising strategy to achieve synergistic efficacy and improve long-term outcomes.

Fullerenes, cage-structured carbon allotropes with extensively delocalized π -conjugated surfaces [19], are known to quench reactive hydroxyl radicals ($\cdot$ OH) and superoxide anions ($\cdot$ O $_2^-$) by delocalizing unpaired electrons across their carbon cage [20]. Water-soluble fullerene derivatives exhibit excellent ROS-quenching capacity, anti-inflammatory activity, and biocompatibility [21–25]. For instance, alanine-modified fullerene dampens systemic inflammation by downregulating the LPS/TLR4/NF- κ B pathway [22], while amino- and hydroxyl-functionalized C $_{60}$ fullerenes embedded in hydrogels alleviate inflammation via ROS elimination [26]. However, many reported derivatives are mixtures of isomers or multi-additive formulations, obscuring structure–activity relationships and hindering drug development. In our previous work, we developed a straightforward synthesis of structurally defined tetraamino-[60]fullerene epoxides (C $_{60}$ (NR'R') $_4$ O) [27]. Among them, tetra [4-(amino) piperidin-1-yl]C $_{60}$ epoxide (TAPC) inhibits cancer cell proliferation by inducing G0/G1 arrest through downregulation of Cyclin D1 [23, 28]. Given the demonstrated antioxidant properties of water-soluble fullerenes and the specific anti-proliferative effect of TAPC, we hypothesized that aminated fullerene derivatives could alleviate psoriasis through multimechanistic actions.

In this study, we prepared and characterized TAPC and tetra (piperazin-1-yl) C $_{60}$ epoxide (TPPC), formulated them into hydrogel vehicles (TAPC@CB and TPPC@CB), and evaluated their therapeutic potential in psoriasis models. These hydrogels inhibited keratinocyte hyperproliferation, scavenged ROS, and alleviated inflammation, collectively reshaping the skin inflammatory microenvironment. Through integrated omics and functional assays, we delineated the underlying molecular mechanisms and demonstrated that TAPC@CB effectively prevents psoriasis relapse, outperforming a clinical comparator. Our findings highlight aminated fullerenes as a versatile nanomaterial platform for multitarget therapy of inflammatory skin diseases.

2 Results and discussion

2.1 Fullerene derivatives inhibit keratinocyte hyperproliferation, scavenge ROS, and modulate macrophage polarization *in vitro*

A HaCaT cell model stimulated with the M5 cytokine cocktail (M5) was used to mimic psoriatic hyperproliferation, quaternary ammonium salt-, PEGylated-, and carboxylated fullerenes (Fig. 1(a) and Fig. S1 in the Electronic Supplementary Material (ESM)). Aminated (TAPC, TPPC, tetra[4-(aminoethyl)piperidin-1-yl]C $_{60}$ epoxide (TAEPCE)) and carboxylated (tetra[4-(carboxyl)piperidin-1-yl]C $_{60}$ epoxide (TCPC), malonic acid-C $_{60}$ bis-adduct (MCBA), malonic acid-C $_{60}$ tetra-adduct (MCTA-2)) derivatives significantly suppressed M5-induced hyperproliferation in a concentration-dependent manner (Fig. 1(b) and Fig. S2 in the ESM). However, carboxylated derivatives either contained isomeric mixtures (MCBA, MCTA-2) or exhibited excessive cytotoxicity (TCPC, Fig. S3 in the ESM). Therefore, TAPC and TPPC, which showed strong anti-proliferative activity with acceptable cytotoxicity, were selected for further study. Consistent with their inhibitory effect, aminated fullerene treatment markedly reduced the proportion of 5-ethynyl-2'-deoxyuridine (EdU)-positive keratinocytes (Fig. 1(c)). Consistent with this anti-proliferative effect, cell-cycle analysis demonstrated that each compound markedly increased the proportion of cells in G0/G1 phase (from approximately 50% to > 80%) while decreasing the fraction in S phase (from ~ 40% to < 20%) (Fig. 1(d) and Fig. S4 in the ESM), indicating effective induction of G0/G1 arrest. Notably, TAPC elicited a more pronounced cell-cycle arrest compared to TPPC.

Given the central role of ROS in psoriasis, we assessed the ROS-scavenging capacity of TAPC and TPPC. Both derivatives effectively eliminated $\cdot$ OH and $\cdot$ O $_2^-$ *in vitro* (Fig. S5 in the ESM) and reduced intracellular ROS in lipopolysaccharide (LPS)-stimulated macrophages (Fig. 1(e) and Fig. S6 in the ESM). Furthermore, flow cytometry showed that TAPC and TPPC decreased the proportion of M1 macrophages (CD86 $^+$) and increased the M2 subset (CD206 $^+$) (Fig. 1(f) and Fig. S7 in the ESM), indicating a shift from pro-inflammatory to anti-inflammatory phenotypes. The results of the Western blot (WB) experiment also confirmed this conclusion (Fig. S8 in the ESM). Moreover, TAPC and TPPC significantly suppressed pro-inflammatory factor expression in RAW264.7 cells, providing direct evidence of their anti-inflammatory effects (Fig. S9 in the ESM). Inflammation microenvironment of psoriasis leads to excessive keratinocyte migration, which could further aggravate psoriasis [29, 30]. In wound-healing assays, both compounds significantly suppressed M5-induced HaCaT migration (Fig. 1(g)), supporting their potential to inhibit psoriasis-associated cellular mobilization.

2.2 Development and function of aminated fullerene hydrogels

For topical delivery, TAPC and TPPC were uniformly dispersed in a carbomer matrix and cross-linked with triethanolamine to form stable hydrogels (TAPC@CB and TPPC@CB; Fig. 2(a)). The resulting hydrogel displayed a homogeneous, colloidal appearance without visible aggregation, indicating excellent dispersion of the fullerenes within the matrix (Fig. 2(b)). Scanning electron microscopy (SEM) revealed a characteristic three-dimensional porous network structure (Fig. 2(c)). Zeta potential measurements

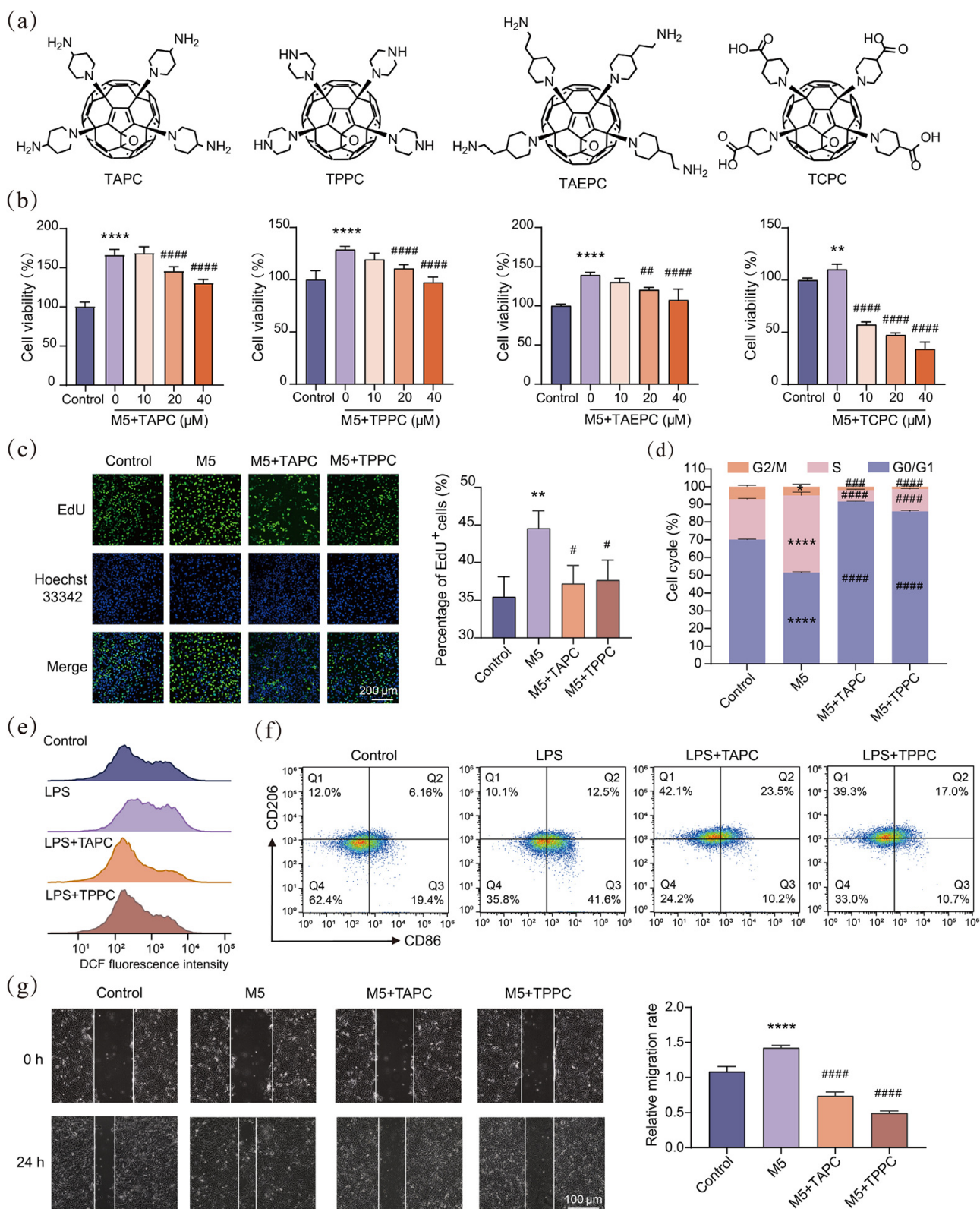


Figure 1 Fullerene derivatives alleviate keratinocyte hyperproliferation, ROS stress, and inflammation. (a) Chemical structures of TAPC, TPPC, TAEPC, and TCPC. (b) Inhibitory effects of TAPC, TPPC, TAEPC, and TCPC on M5-induced hyperproliferation of HaCaT cells ($n = 6$). (c) Left: Representative fluorescence images of HaCaT cells (EdU assay) under indicated treatments (scale bar = 200 μm). Right: Quantification of EdU-positive cells ($n = 3$). (d) Cell-cycle distribution of HaCaT cells after treatment with TAPC or TPPC. (e) Intracellular ROS levels in RAW264.7 macrophages measured by flow cytometry after LPS stimulation with or without fullerene treatment. (f) Expression of the M1 marker CD86 and M2 marker CD206 on RAW264.7 macrophages assessed by flow cytometry. (g) Left: Representative images of HaCaT cell migration in a wound-healing assay after treatment with TAPC or TPPC (scale bar = 100 μm). Right: Quantification of wound closure ($n = 3$). Data are presented as mean $\pm$ standard error of the mean (s.e.m.). Statistical significance was determined by one-way ANOVA with Tukey's multiple comparisons test: * $P < 0.01$, ** $P < 0.01$, and *** $P < 0.0001$ vs. control; * $P < 0.05$, # $P < 0.01$, ## $P < 0.001$, ### $P < 0.0001$ vs. M5/LPS group.

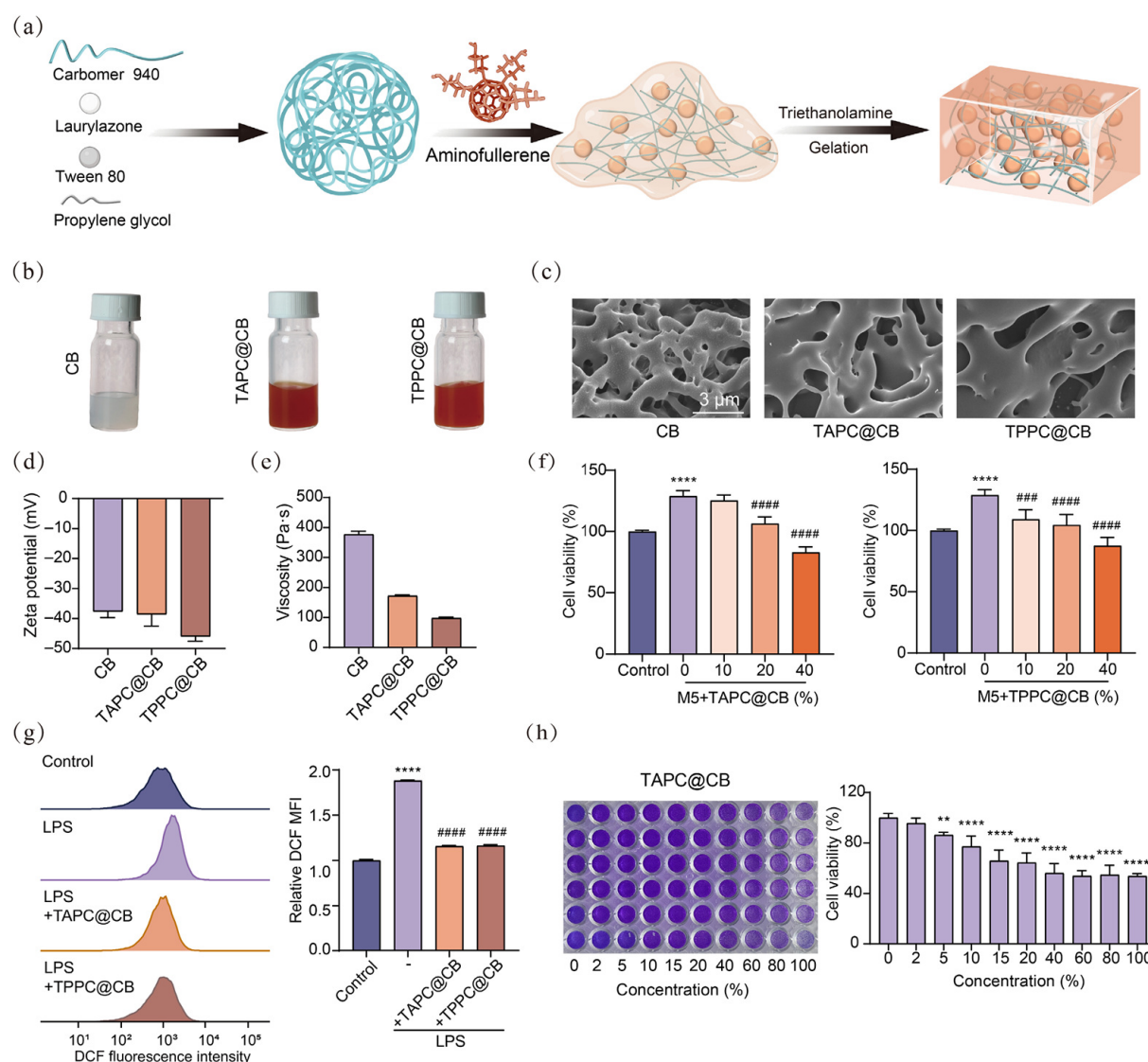


Figure 2 Preparation and characterization of aminated fullerene hydrogels and their activity *in vitro*. (a) Schematic illustration of the fabrication of TAPC@CB and TPPC@CB hydrogels. (b) Optical images and (c) representative SEM micrographs of CB, TAPC@CB, and TPPC@CB (scale bar = 3 μm). (d) Zeta potential and (e) viscosity profiles of CB, TAPC@CB, and TPPC@CB ($n = 3$). (f) Inhibitory effects of extract solutions from TAPC@CB and TPPC@CB on M5-induced hyperproliferation of HaCaT cells ($n = 6$). (g) Flow cytometric quantification of intracellular ROS levels in LPS-stimulated RAW264.7 macrophages following treatment with indicated formulations ($n = 3$). (h) Cytotoxicity assessment of TAPC@CB extract solution toward HaCaT cells. Left: Crystal violet staining. Right: Quantitative results of crystal violet dissolution ($n = 6$). Data are presented as mean $\pm$ s.e.m. Statistical analysis was performed using one-way ANOVA with Tukey's multiple comparisons test: $P < 0.05$, $^{*}P < 0.01$, $^{**}P < 0.001$, and $^{***}P < 0.0001$ vs. the control group; $^{*}P < 0.001$ and $^{***}P < 0.0001$ vs. M5/LPS group.

demonstrated a strongly negative surface charge, ranging from -35 to -49 mV (Fig. 2(d)), which is expected to facilitate electrostatic interaction with cationic aminated fullerenes and support sustained drug release.

Viscosity, which reflects the fluidity and extensibility of the hydrogel, is influenced by macromolecular architecture—branched structures can reduce fluid viscosity [31]. The viscosities of TAPC@CB and TPPC@CB ranged between 100 and 200 Pa·s (Fig. 2(e)), significantly lower than that of the blank carbomer hydrogel (> 300 Pa·s). This reduction may be attributed to the branched configuration of TAPC and TPPC, which can intercalate into the carbomer network, disrupting linear chain entanglement and loosening the overall gel structure. The moderate viscosity ensures adequate adhesion to psoriatic plaques.

Hydrogel stability underpins pharmacological performance and

clinical utility [32]. The hydrogels demonstrated excellent stability: hydrodynamic diameters varied $< 3\%$ over 30 days (Fig. S10 in the ESM), and pH remained stable at 6.5–7.0 (Fig. S11 in the ESM). Extract solutions of TAPC@CB and TPPC@CB retained the anti-proliferative (Fig. 2(f) and Fig. S12 in the ESM) and ROS-scavenging (Fig. 2(g)) activities of the free compounds, with comparable cytotoxicity profiles (Fig. 2(h) and Fig. S13 in the ESM), confirming that the hydrogel formulation preserved bioactivity.

2.3 TAPC@CB and TPPC@CB alleviate psoriasis *in vivo*

To evaluate the therapeutic efficacy of TAPC@CB and TPPC@CB on psoriatic lesions, a psoriasis-like mouse model was established using topical imiquimod (IMQ) cream. BALB/c mice received a daily application of 62.5 mg IMQ cream in the morning to induce psoriatic phenotypes, followed by afternoon treatments with

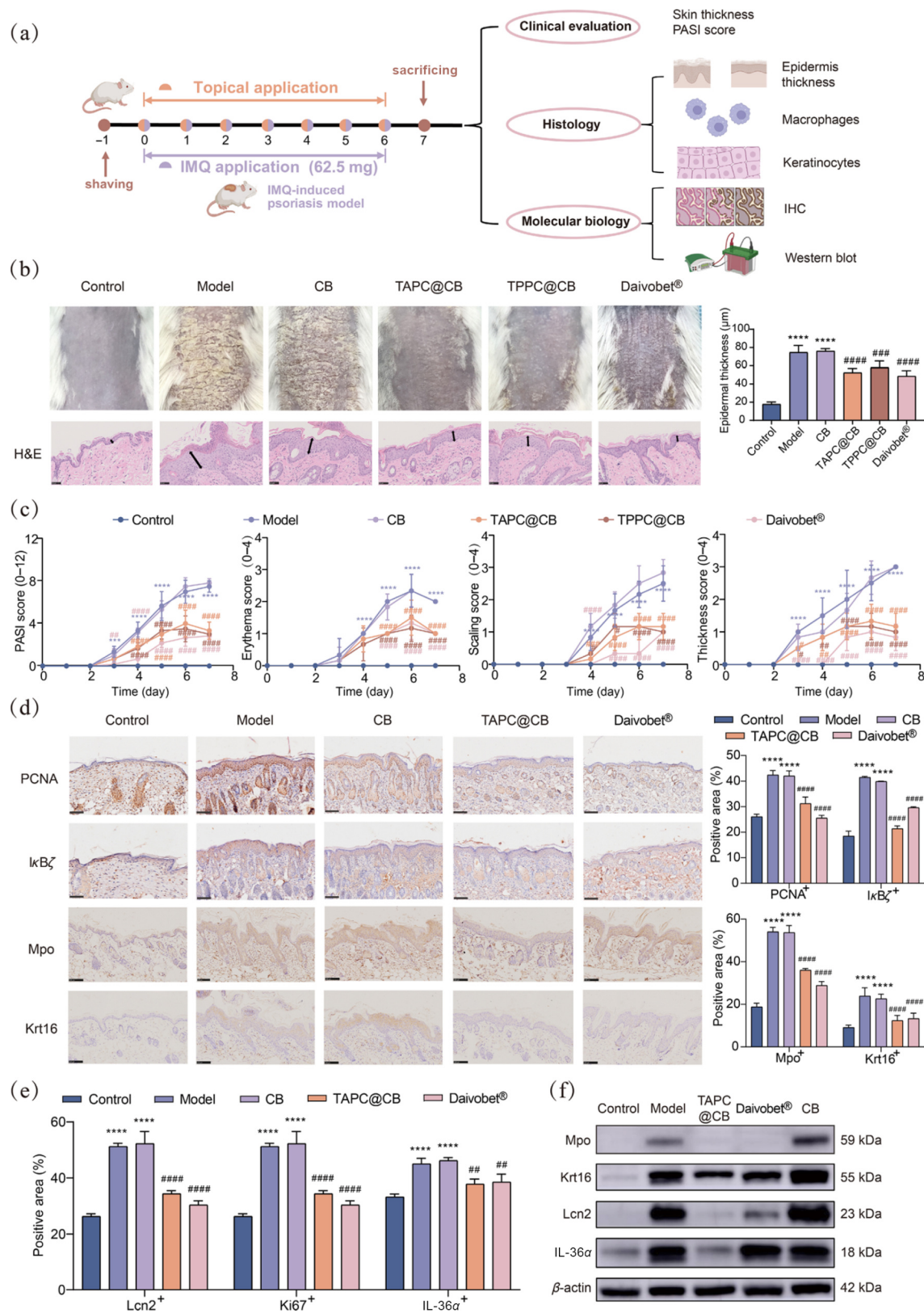


Figure 3 *In vivo* therapeutic efficacy of aminated fullerene hydrogels in an IMQ-induced psoriasis model. (a) Schematic of the experimental design, including psoriasis induction, treatment regimen, and efficacy assessment. (b) Left: Representative photographs of dorsal skin and corresponding H&E-stained sections on day 7 (scale bars = 50 μ m, black arrows indicated the mouse skin thickness). Right: Quantitative analysis of epidermal thickness ($n = 6$). (c) PASI scores throughout the treatment period ($n = 6$). (d) Left: Immunohistochemical staining of PCNA, IκB ζ , Mpo, and Krt16 in skin sections on day 7 (scale bars = 100 μ m). Right: Quantitative analysis of staining intensity ($n = 3$). (e) Quantitative analysis of immunohistochemical staining for Lcn2, Ki67, and IL-36 α in skin lesions ($n = 3$). (f) Western blot analysis of Mpo, Krt16, Lcn2, and IL-36 α protein expressions in skin tissues. Data are presented as mean $\pm$ s.e.m. Statistical analysis was performed using one-way ANOVA with Tukey's multiple comparisons test: *** $P < 0.001$ and **** $P < 0.0001$ vs. the control group; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ and **** $P < 0.0001$ vs. the model group.

TAPC@CB or TPPC@CB for seven consecutive days (Fig. 3(a)). Animals were randomly allocated into six groups: control, IMQ-induced model, model treated with blank CB, TAPC@CB, TPPC@CB, and Daivobet® as a positive control. Throughout the treatment period, body weight remained stable across all groups (Fig. S14 in the ESM).

Epidermal hyperplasia, a hallmark of psoriasis, was assessed via representative clinical images and hematoxylin & eosin (H&E)-stained skin sections (Fig. 3(b)). The model and CB-treated groups exhibited pronounced psoriatic features, including erythema, marked skin thickening, and scaling. In contrast, treatment with TAPC@CB, TPPC@CB, or Daivobet® significantly alleviated these clinical symptoms. Both fullerene hydrogels effectively mitigated IMQ-induced epidermal hyperplasia, acanthosis, and hyperkeratosis, showing efficacy comparable to Daivobet®. Consistent with morphological improvements, Psoriasis Area and Severity Index (PASI) scores were significantly elevated in the model and CB groups relative to controls, and were markedly reduced following treatment with TAPC@CB or TPPC@CB (Fig. 3(c)). Together, these findings indicate that TAPC@CB and TPPC@CB effectively reversed IMQ-induced psoriatic lesions and histological abnormalities, underscoring their therapeutic potential.

To elucidate the underlying mechanisms, immunohistochemical (IHC) analysis was performed on key pathophysiological markers related to proliferation, inflammation, and differentiation (Fig. 3(d)). Proliferating cell nuclear antigen (PCNA), an indicator of epidermal cell proliferation, was highly expressed in the nuclei of basal and spinous layer keratinocytes in the model group. This expression was substantially reduced after TAPC@CB treatment. Similarly, another proliferation marker, Ki67, was significantly downregulated (Fig. 3(e) and Fig. S16 in the ESM), confirming inhibition of keratinocyte hyperproliferation.

The transcriptional regulator I κ B ζ , which amplifies proinflammatory cytokine production within the NF- κ B pathway and sustains inflammatory cascades in psoriasis [33, 34], showed strong nuclear expression in model group keratinocytes. TAPC@CB treatment significantly decreased I κ B ζ levels, indicating suppression of inflammatory signaling. Myeloperoxidase (Mpo), a marker for neutrophil infiltration associated with microabscess formation, revealed abundant positive cells beneath the stratum corneum in model mice, corroborating H&E observations of extensive neutrophil influx. TAPC@CB treatment markedly reduced Mpo⁺ cells, reflecting diminished inflammatory infiltration. Furthermore, keratin 16 (Krt16), a marker of aberrant differentiation and hyperproliferation, displayed high cytoplasmic expression in the model epidermis, which was notably attenuated by TAPC@CB, suggesting promotion of normal keratinocyte differentiation. Malondialdehyde (MDA), a hallmark of ROS-induced oxidative damage, was significantly elevated in psoriatic lesions of model and CB groups, confirming oxidative stress involvement. TAPC@CB treatment markedly reduced MDA levels (Fig. S17 in the ESM), demonstrating its antioxidant efficacy via inhibition of lipid peroxidation and mitigation of tissue damage.

Western blot analysis further validated these findings, demonstrating that TAPC@CB downregulated the inflammatory mediators IL-36 α and lipocalin-2 (Lcn2), the neutrophil marker Mpo, and the keratinization marker Krt16 (Fig. 3(f)). Collectively, these results confirm that TAPC@CB alleviates both hyperproliferation and inflammation in psoriatic skin.

In summary, TAPC@CB exerts its therapeutic effects by

concurrently inhibiting keratinocyte hyperproliferation, attenuating inflammatory responses, and promoting the normalization of epidermal differentiation. This multifaceted action effectively disrupts the vicious cycle between abnormal proliferation and inflammation, targeting core pathological features of psoriasis.

2.4 Integrated transcriptomic–proteomic profiling identifies key regulators

To further explore the molecular basis underlying the therapeutic effects of aminated fullerenes, we performed transcriptome sequencing and proteomic profiling on the skin lesions of mice with psoriatic dermatitis induced by IMQ. The analysis was aimed at identifying key regulatory molecules that satisfied three criteria simultaneously: exhibiting disease-associated transcriptional trends reversed by treatment, displaying significant protein-level differences in both Model vs. Control and TAPC@CB vs. Model comparisons, and showing a consistent direction of change between RNA and protein layers.

Transcriptomic data were first subjected to Mfuzz (Fuzzy C-Means Clustering Algorithm) soft clustering to group genes with similar dynamic patterns (see section 4.22), resulting in ten distinct expression clusters (Fig. 4(a) and Fig. S18 in the ESM). Among these, clusters 3, 5, 9, and 10 demonstrated clear reversal toward the healthy expression state after fullerene treatment (Fig. 4(a)), indicating that they captured psoriasis-related transcriptional programs responsive to TAPC@CB. Parallel proteomic analysis identified differentially expressed proteins (DEPs) using significant thresholds ($P < 0.05$ and $|\log_2 FC| \geq 1$), and proteins altered in both Model vs. Control and TAPC@CB vs. Model were retained for downstream interpretation. Volcano plots visualized the distribution of these changes, and Kyoto Encyclopedia of Genes and Genomes/Gene Ontology (KEGG/GO) enrichment analyses revealed that IMQ-induced alterations were strongly associated with canonical psoriasis pathways, including cornified envelope formation, cytokine–receptor signaling, NF- κ B activation, IL-6-mediated inflammatory responses, myeloid immune activation, and lipid metabolic imbalance. In contrast, proteins reversed by TAPC@CB were mainly enriched in pathways related to immune regulation, epithelial homeostasis, and metabolic restoration, suggesting that fullerene treatment mitigates both abnormal differentiation and excessive inflammation in psoriatic lesions (Fig. S19 in the ESM).

To maximize retention of potential regulatory targets, all proteins with $P < 0.05$ in both comparisons were merged, yielding a set of 299 proteins exhibiting significant and opposite changes between Model vs. Control and TAPC@CB vs. Model (Fig. 4(b)). These proteins were intersected with the reversible Mfuzz clusters (3, 5, 9, 10), and candidates with consistent RNA–protein directions were subjected to GO functional interpretation. Cluster 3 was primarily enriched in processes related to fatty acid biosynthesis and metabolism, epithelial proliferation control, and intercellular communication, indicating that TAPC@CB may alleviate keratinocyte hyperproliferation and epidermal barrier disruption by restoring epidermal metabolic homeostasis and epithelial signaling integrity (Fig. 4(c)). Cluster 9 was predominantly associated with inflammatory responses, chemotaxis, and apoptosis, suggesting that treatment ameliorates chronic immune infiltration and cytokine overactivation by reshaping inflammatory gene programs (Fig. 4(d)).

Integrating subcellular localization, functional annotations, and expression reversibility allowed us to pinpoint four proteins—S100

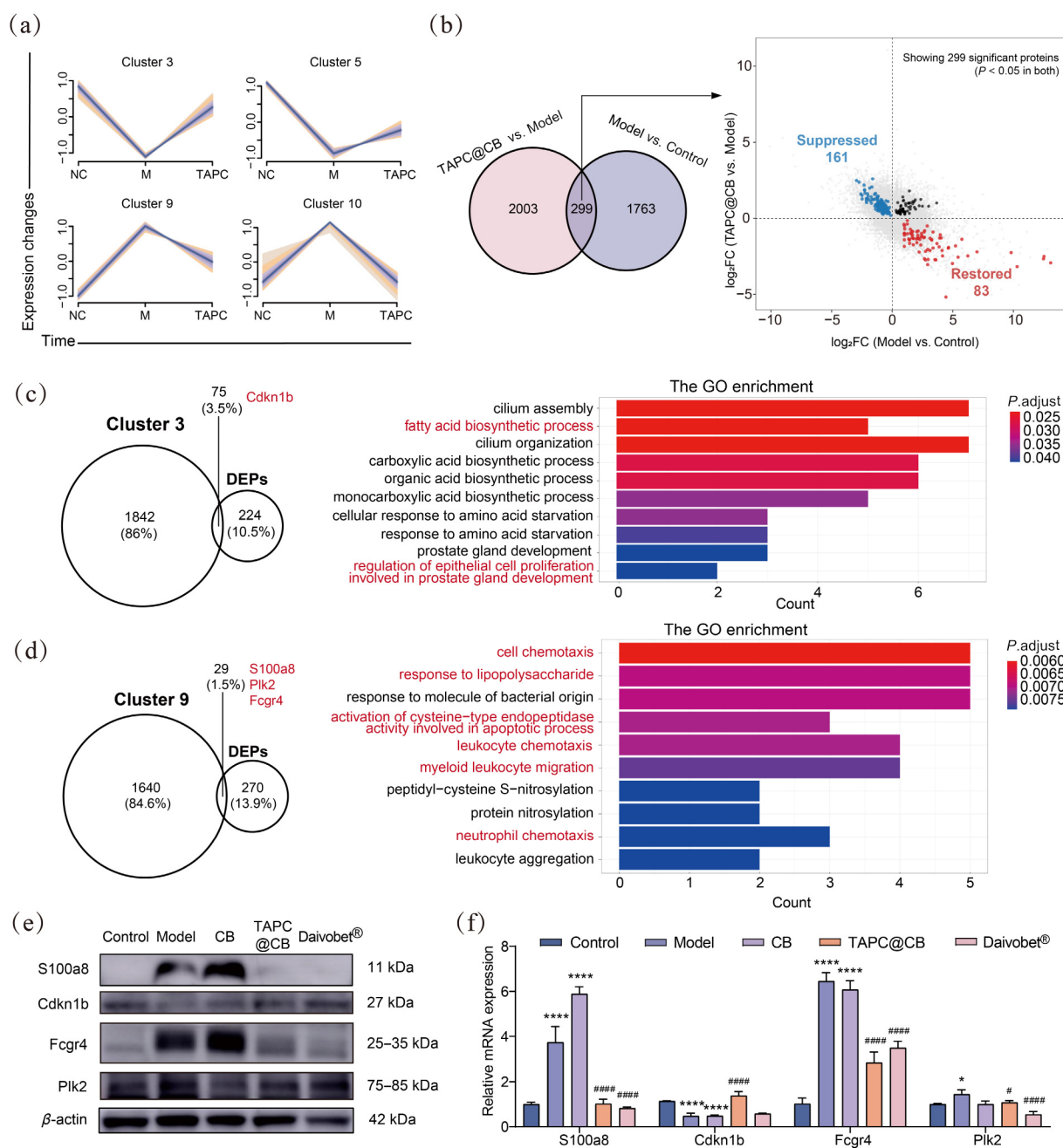


Figure 4 Multiomics analysis of mouse skin lesions and the identification of crucial regulators. (a) Gene expression clusters that reverse to a healthy expression state. (b) Venn diagram of proteomic targets (Left) and scatter plot (Right) of overlapping proteins. Points are color-coded by regulation pattern: red indicates suppressed proteins (model up/treatment down), blue indicates restored proteins (model down/treatment up), and black indicates significant but non-reversed proteins. (c) Screening and functional annotation of cross-omics molecules in cluster 3. (d) Screening and functional annotation of cross-omics molecules in cluster 9. (e) RT-qPCR and (f) WB analysis of S100a8, Cdkn1b, Fcgr4, and Plk2 in skin lesions of mice from different groups ($n = 3$). Data are presented as mean $\pm$ s.e.m. Statistical analysis was performed using one-way ANOVA with Tukey's multiple comparisons test: *** $P < 0.001$, and **** $P < 0.0001$ vs. the control group; * $P < 0.001$ and **** $P < 0.0001$ vs. the model group.

calcium binding protein A8 (S100a8), Fc gamma receptor IV (Fcgr4), Polo-like kinase 2 (Plk2), and Cyclin-dependent kinase inhibitor 1B (Cdkn1b)—as core regulators mediating the therapeutic response to TAPC@CB. Western blotting confirmed that S100a8 and Fcgr4, two inflammation-associated proteins aligned with cluster 9 signatures, were markedly suppressed following treatment (Fig. 4(e)), consistent with the reduction of excessive myeloid activation and inflammatory infiltration in psoriatic lesions. Plk2, a kinase linked to stress signaling, was also downregulated, potentially contributing to the attenuation of

inflammatory signaling and the indirect restraint of keratinocyte over-activation [35]. Conversely, Cdkn1b was significantly upregulated and matched the epithelial-homeostasis signature of cluster 3; as a G1-phase inhibitory protein, its increased expression provides a mechanistic explanation for the normalization of keratinocyte proliferation and the restoration of epidermal differentiation [36, 37]. Reverse transcription quantitative polymerase chain reaction (RT-qPCR) further validated RNA–protein concordance for these key molecules (Fig. 4(f)).

Together, these multiomics findings delineate a coherent

mechanism through which aminated fullerenes exert therapeutic efficacy in psoriasis. By repressing inflammation-related proteins and re-establishing immune balance, while simultaneously restoring cell-cycle control and epidermal metabolic stability, TAPC@CB coordinates a multitarget regulatory response that effectively reverses core pathological processes in psoriatic skin.

2.5 TAPC@CB prevents psoriasis relapse

A psoriasis relapse model was established in mice by administering a secondary, lower-dose IMQ regimen for 7 days, following an

initial 7-day induction phase and a subsequent 15-day rest period (Fig. 5(a)). During the rest interval, skin thickening gradually resolved across all groups. However, upon re-stimulation with IMQ for 7 days, erythema and scaling re-emerged in mice from various treatment groups, accompanied by increased epidermal thickness (Fig. 5(b) and Fig. S15 in the ESM). Notably, mice previously treated with TAPC@CB exhibited only mild psoriasis-like lesions upon relapse, whereas those treated with Daivobet® showed limited preventive efficacy against disease recurrence (Fig. 5(c)).

In psoriasis relapse, macrophages contribute to the initiation and

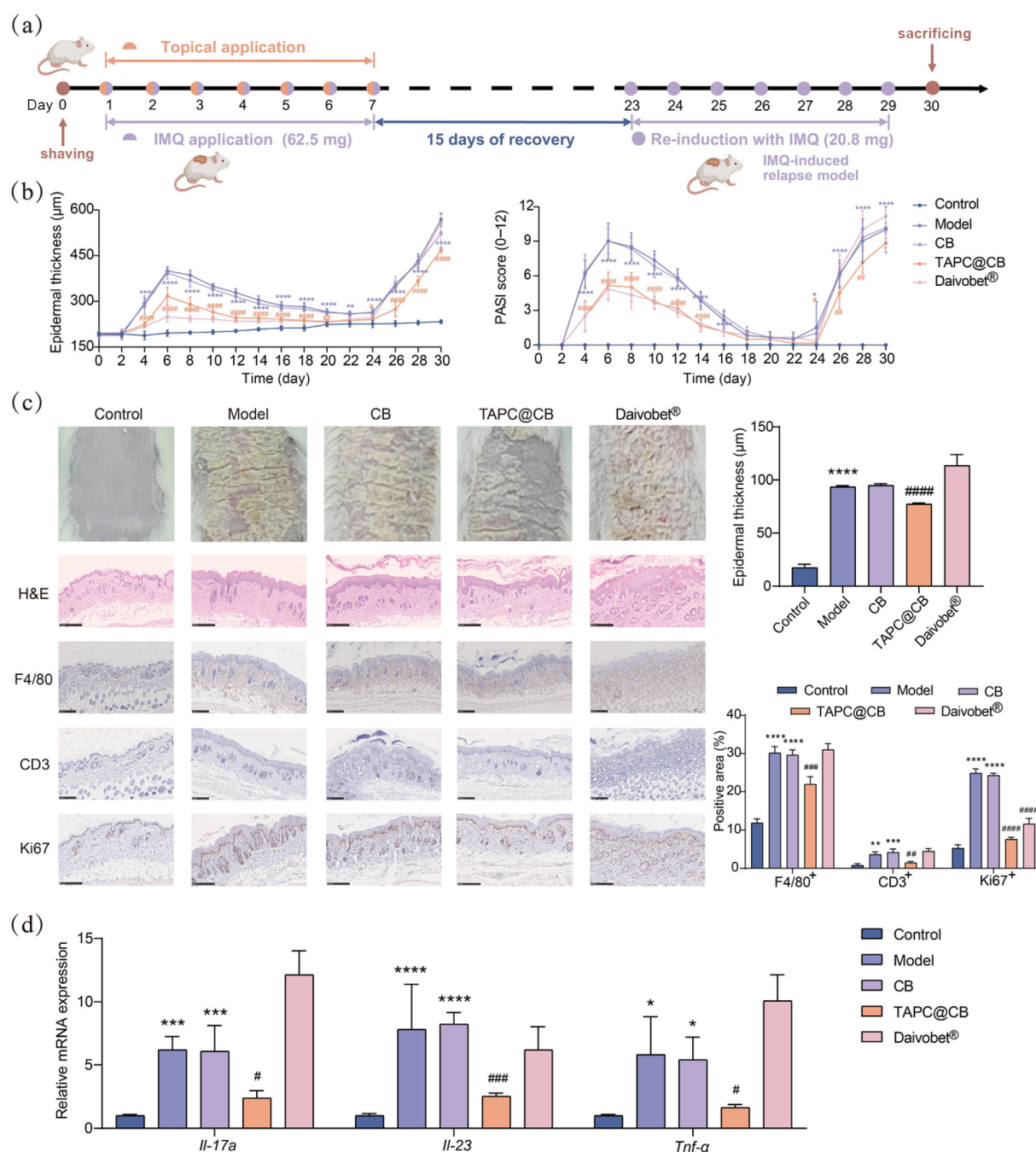


Figure 5 TAPC@CB alleviates psoriasis relapse *in vivo*. (a) Schematic of the IMQ-induced psoriasis relapse model. (b) Quantification of back-skin thickness (left) and PASI scores (right) over 30 days ($n = 6$). (c) Left: Representative photographs of skin lesions, H&E staining, and immunohistochemical staining for F4/80 and CD3 (scale bars = 250 μm). Right: Quantitative analysis of epidermal thickness and immunohistochemical ($n = 3$). (d) The mRNA expression levels of *IL-17a*, *IL-23* and *Tnf-α* of skin lesions from each group ($n = 3$). Data are presented as mean $\pm$ s.e.m. Statistical analysis was performed using one-way ANOVA with Tukey's multiple comparisons test: *** $P < 0.001$, and **** $P < 0.0001$ vs. the control group; * $P < 0.001$ and **** $P < 0.0001$ vs. the model group.

maintenance of the inflammatory microenvironment by releasing pro-inflammatory factors such as TNF- α and IL-23, while activated T cells drive antigen-specific immune responses—collectively exacerbating disease progression [8]. To evaluate these mechanisms, we examined macrophage and T-cell markers along with associated pro-inflammatory cytokines. IHC analysis revealed that, compared with the non-relapse group, lesional skin from IMQ-, CB-, and Daivobet®-treated mice displayed significantly increased numbers of F4/80⁺ macrophages (in the dermis) and CD3⁺ T cells (beneath the epidermis and in the dermis). These increases were markedly downregulated by TAPC@CB treatment (Fig. 5(c)). Furthermore, mRNA levels of the inflammatory cytokines *Il-17a*, *Il-23* and *Tnf- α* in lesional skin were also significantly reduced following TAPC@CB administration (Fig. 5(d)).

Together, these findings demonstrate that TAPC@CB exerts a sustained therapeutic effect against psoriasis relapse. This action is mediated through multiple pathways, including attenuation of epidermal hyperplasia, downregulation of key pro-inflammatory cytokines (notably IL-17A, IL-23, and TNF- α), and suppression of pathogenic activation and recruitment of T cells and macrophages. These coordinated mechanisms underlie a relapse-preventive potential that surpasses that of Daivobet®.

3 Conclusions

In summary, this study demonstrates that the aminated fullerene derivatives TAPC and TPPC—both in free form and as hydrogel formulations—can effectively ameliorate psoriasis through a single-agent, multitarget mechanism. This mechanism encompasses the regulation of oxidative stress, suppression of excessive inflammatory activation, and inhibition of abnormal keratinocyte proliferation. Specifically, TAPC and TPPC significantly suppressed M5-induced keratinocyte hyperproliferation by inducing G0/G1 cell-cycle arrest and markedly inhibited keratinocyte migration. Moreover, in inflammatory macrophages, these compounds effectively scavenged excess ROS and promoted polarization from the pro-inflammatory M1 phenotype toward the anti-inflammatory M2 phenotype, thereby improving the psoriatic inflammatory microenvironment.

In vivo, topical application of TAPC@CB significantly reduced the PASI score, epidermal hyperplasia, and inflammatory infiltration in an IMQ-induced psoriasis mouse model. TAPC@CB treatment downregulated key markers of keratinocyte proliferation (PCNA and Ki67) and neutrophil activation (Mpo and Lcn2), thereby restraining abnormal epidermal growth and inflammatory responses. Furthermore, it suppressed the release of pro-inflammatory cytokines by inhibiting the NF- κ B signaling pathway. Integrated transcriptomic and proteomic analyses identified several key regulatory factors—S100a8, Fcgr4, Plk2, and Cdkn1b—whose expression levels were reversed following TAPC@CB treatment. This suggests that amino-fullerene derivatives remodel the inflammatory microenvironment and restore skin homeostasis by modulating multiple gene networks. TAPC@CB demonstrated a more sustained therapeutic effect than the clinical comparator Daivobet®. It effectively reduced macrophage and T cell infiltration in psoriatic lesions, significantly alleviated inflammation, and lowered the risk of disease relapse.

Collectively, this work highlights that aminated fullerene derivatives exert their therapeutic effects through synergistic, multitarget, and multipathway regulation, offering a novel strategic

direction for psoriasis treatment research. In contrast to conventional combination therapies, this single-agent, multimechanism approach simplifies treatment regimens, may improve patient compliance, and reduce risks associated with drug–drug interactions. By systematically remodeling the disease microenvironment rather than targeting isolated pathological processes, this strategy holds promise for achieving more fundamental and durable therapeutic outcomes. Conventional topical therapies (e.g., corticosteroids) have limited efficacy and local side effects; systemic agents (e.g., methotrexate) cause severe off-target toxicity; biologics (e.g., TNF- α inhibitors) are costly and prone to resistance. The fullerene derivatives avoid these drawbacks by their multitarget mode but have limitations: unclear long-term safety, ambiguous precise molecular targets, and reliance on preclinical data. Future studies should focus on further chemical optimization of these derivatives, elucidation of their precise molecular targets and signaling networks, evaluation of their long-term safety and potential resistance development, and ultimately, translation toward clinical application.

4 Experimental

4.1 Materials and reagents

All chemicals and reagents were obtained from the indicated suppliers and used without further purification. C₆₀ (purity > 99.5%) was purchased from Beijing Funatech Co., Ltd. (China). 4-N-Boc-aminopiperidine, 4-(tert-butyl) piperidine-1-carboxylate, and trifluoroacetic acid (TFA) were obtained from Nanjing Innochem Science & Technology Co., Ltd. (China). Cumene hydroperoxide (CHP, 80%), d-biotin N-succinimidyl ester, and dimethyl sulfide were sourced from Shanghai Aladdin Biochemical Technology Co., Ltd. (China). Polyethylene glycol (PEG, $M_w \sim 1900$) and phosphorus oxychloride were acquired from Alfa Aesar (China) Chemical Co., Ltd. (China). d-Luciferin potassium salt (luciferin) and the Cell Counting Kit-8 (CCK-8) were supplied by Yeasen Biotechnology (Shanghai) Co., Ltd. (China). The EdU-488 Kit, Cell Cycle Kit, ROS Assay Kit, ELISA Kit and BCA Protein Assay Kit were purchased from Beyotime Biotechnology (China). The 2',7'-dichlorodihydrofluorescein diacetate (DCFH-DA) fluorescent probe was purchased from MCE (USA). LPS was obtained from Sigma-Aldrich (USA). Antibodies against CD86 and CD206 for flow cytometry were procured from Thermo Fisher Scientific (USA). RNA-easy Isolation Reagent was obtained from Nanjing Novonta (China). Primary antibodies for WB and IHC were obtained from Wuhan San Ying Biotechnology/Proteintech Group (China). IMQ was obtained from Sichuan Mingxin Lidi Pharmaceutical Co., Ltd. (China). Daivobet® was purchased from LEO Pharma (Denmark).

4.2 Material synthesis

Synthesis of tetrasubstituted epoxidized fullerenes TAPC, TPPC, TAEP, TCPC: according to literature reports [38], C₆₀Cl₆ was first synthesized. To a toluene solution of C₆₀Cl₆, anhydrous K₂CO₃, 80% CHP, and structurally distinct modifying groups were successively added. The reaction mixture was stirred at room temperature for 0.5–2 h. The organic phase was then washed sequentially with saturated aqueous NH₄Cl solution and aqueous NaHCO₃ solution. After drying over anhydrous Na₂SO₄, the crude product was purified by silica gel column chromatography, using a mixture of

toluene and ethyl acetate as the eluent. Bright orange solutions corresponding to TAPC, TPPC, TAEP, and TCPC were obtained from the chromatographic column.

Synthesis of C_{60} -(N,N-dimethyl-pyrrolidinium iodide) (NDMPFI) and C_{60} -(N-methyl-N-benzyl-pyrrolidinium iodide) (NMBPFI): C_{60} and toluene were added to a three-necked round-bottom flask and stirred until clear. Sarcosine or N-benzylglycine (for NDMPFI or NMBPFI) and paraformaldehyde were then added. The system was purged with nitrogen gas and the mixture was heated under reflux for 5–6 h. After cooling to room temperature, the solution was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford a black crude product. Unreacted C_{60} was removed on a silica hydrogel column using a mixture of n-hexane and toluene as the eluent. The target compound was subsequently eluted with toluene, yielding a black solid. This solid was vacuum-dried for 24 h to obtain the intermediate (C_{60} -(N-methyl-pyrrolidinium) (NMPF) or C_{60} -(N-benzyl-pyrrolidinium) (NBPF)). Each intermediate was then combined with iodomethane in a single-necked round-bottom flask and stirred at room temperature for 48 h. The resulting precipitate was collected by filtration, washed with toluene and o-dichlorobenzene, and vacuum-dried for 24 h to give NDMPFI or NMBPFI as a brown solid.

Synthesis of FPEG₄: $C_{60}Cl_6$ was dissolved in toluene, anhydrous sodium carbonate was added and stirred at room temperature for 30 min, then an appropriate amount of aminopentaethylene glycol monomethyl ether was added; After stirring at room temperature for 1 day, the upper clear liquid was concentrated and evaporated to dryness to obtain a reddish-brown solid product.

Synthesis of MCBA, MCTA-1, and MCTA-2: C_{60} was fully dissolved in toluene, followed by the addition of 1 molar equivalent of di-tert-butyl malonate, trace amounts of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and CBr_4 . The reaction was carried out at room temperature for 8 h. After completion, the mixture was extracted with water, dried over Na_2SO_4 , and concentrated under reduced pressure. Pure toluene was used to separate the reddish-brown product di-tert-butyl malonate- C_{60} tris-adduct (DCTA-1) on a silica hydrogel column. DCTA-1 was dissolved in 40 mL of toluene, and an equal amount of trifluoroacetic acid was added. After stirring for 2 h, the solvent was removed under reduced pressure. The product was washed with toluene and dried to obtain MCTA-1. Using the same reaction conditions, the molar equivalent of di-tert-butyl malonate was increased to 3 and 4, respectively, to obtain malonic acid- C_{60} tris-adduct (MCTA-1) and malonic acid- C_{60} tetra-adduct (MCTA-2). The designations MCTA-1 and MCTA-2 are used solely to distinguish between these two molecules.

4.3 Hydrogel preparation

The aminated fullerene hydrogel was prepared by mixing aminated fullerene, Carbomer 940 (Innochem, A60397, Beijing, China), propylene glycol (Innochem, A58153, Beijing, China), lauryl nitroxide (Macklin, A800359, Shanghai, China), Tween 80, and triethanolamine. The hydrogel was prepared using a ratio of 0.5% Carbomer 940, 20% propylene glycol, 1% lauryl nitroxide, and 1% Tween 80 (more details are provided in sections S1 and S2 in the ESM). Finally, the pH was adjusted with triethanolamine to form the hydrogel. The final concentration of aminated fullerene was 2 mM in hydrogel.

4.4 Characterization of hydrogel

The macroscopic appearance, color and shape of the hydrogel were observed and recorded by naked eye and optical camera. The morphology of hydrogel was characterized by SEM (G3 CX, Thermo Fisher Scientific, USA). A dynamic light scattering instrument (DLS, NanoZs Zen3600, Malvern, UK) was used to measure the hydrated diameter and zeta potential of the material at 25 °C. The pH value of the hydrogel was measured with a pH meter (PB-10, Sartorius, Germany) at 25 °C. The viscosity of the hydrogel was tested at 25 °C using a rheometer (ARES-G2, TA Instruments, USA). The stability of the hydrogel on the days 1, 3, 5, 7, 15 and 30 was determined by a dynamic light scattering instrument and a pH meter at 25 °C.

4.5 Cell lines and culture

The immortalized human epidermal cell line HaCaT (SUNNCELL) was cultured in Dulbecco's modified Eagle medium (DMEM) containing 10% fetal bovine serum (FBS, Gibco, USA) at 37 °C in a 5% CO_2 atmosphere. After constructing a psoriasis-like keratinocyte model by exposing cells to M5 cytokines (TNF- α , IL-1 α , IL-17A, IL-22, and antitumorogenic factor oncostatin M, each at a concentration of 2.5 ng/mL; Novoprotein Scientific Inc.) [39]. HaCaT cells were treated with different concentrations (0–100 μ M) of fullerene derivatives.

Mouse macrophages leukemia cell (RAW264.7) was purchased from Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences (Beijing, China). RAW264.7 cells were cultured in DMEM medium with 10% fetal bovine serum (Gibco, USA) at 37 °C in a 5% CO_2 atmosphere. RAW264.7 cells were induced to the inflammatory type with LPS and treated with different concentrations (0–100 μ M) of fullerene derivatives.

4.6 Hydrogel extraction solution preparation

Under sterile conditions, 1 mL of hydrogel was placed in a transwell chamber and submerged in a six-well plate containing 2 mL of DMEM with 10% FBS. The mixture was then incubated in a 37 °C, 5% CO_2 incubator for 48 h to ensure complete release. After extraction, the supernatant was collected by centrifugation at 1000g for 10 min, filtered through a 0.22 μ m microporous membrane for sterilization, and the resulting liquid served as the original extract of the gel at 100% concentration, stored at 4 °C. The concentration of subsequent cell experiment was expressed as a percentage of the extract solution.

4.7 In vitro cell viability

HaCaT cells were cultured normally at 1×10^4 per well in a 96-well plate for 24 h, then treated with samples at concentrations ranging from 0 to 100 μ M. Cell viability was detected using the CCK-8 assay kit (Solarbio, CA1210). Absorbance values were measured at 450 nm using an iMark microplate reader (Bio-RAD, USA), and cell activity was calculated (Eq. (1)).

$$\text{Cell viability (\%)} = \frac{OD_{\text{treated}} - OD_{\text{blank}}}{OD_{\text{control}} - OD_{\text{blank}}} \times 100\% \quad (1)$$

where OD_{treated} represents the absorbance of treated cells at 450 nm, OD_{control} represents the absorbance of the control group cells, and OD_{blank} represents the absorbance of the cell-free medium.

4.8 EdU staining

HaCaT cells were cultured using the above medium. After normal culture for 24 h at a density of 5×10^5 cells per well in confocal dishes, the cells were treated with different concentrations of samples for 24 h. Cell proliferation was assessed using the EdU-488 Cell Proliferation Assay Kit, and all experimental procedures were performed according to the manufacturer's instructions. Finally, fluorescent images of labeled cells were captured using a confocal microscope. At least three independent fields of view were selected to ensure the reliability of the results, and the proportion of fluorescent-positive cells was quantitatively analyzed using ImageJ software.

4.9 Wound healing assay

HaCaT cells were seeded in 6-well plates at a density of 5×10^5 cells per well and cultured until > 90% confluence was achieved. Uniform linear scratches were generated in the cell monolayer using a sterile 200 μ L pipette tip (three parallel scratches per well with consistent spacing). The wells were gently washed three times with PBS to remove dislodged cells, followed by treatment with either M5 cytokine cocktail or aminated fullerene derivatives. The plates were then incubated under standard conditions (37 °C, 5% CO₂). Wound closure was monitored at 0 h (baseline) and 24 h post-scratch using an inverted phase-contrast microscope, with images captured at predetermined positions to ensure spatial consistency. Repeat each experiment three times. Migration rates were quantified by measuring the reduction in scratch area using ImageJ software.

4.10 Cell cycle assay

HaCaT cells were cultured at a density of 5×10^5 cells per well in a 6-well plate for 24 h, followed by treatment with the aforementioned samples at different concentrations for 24 h. The cells were then fixed and stained using a Cell Cycle Kit, and the fluorescent signals of cells in each phase were detected using a flow cytometer. The distribution ratios of cells in the G0/G1 phase, S phase, and G2/M phase were analyzed. Each experiment was repeated three times.

4.11 ROS scavenging activity

To assess intracellular ROS levels, RAW264.7 cells were treated with LPS (1 μ g/mL) in the presence or absence of aminated fullerene for 4 h. The cells were then incubated with the ROS-sensitive fluorescent probe DCFH-DA, and the fluorescence intensity was measured by flow cytometry. Three independent experiments were conducted, with a minimum of 20,000 events recorded per sample.

4.12 Macrophages polarization analysis

RAW264.7 cells were treated with LPS (100 ng/mL) in the presence or absence of aminated fullerene for 24 h to establish an inflammatory macrophages model. Following treatment, cells were harvested and stained with fluorescently-labeled antibodies against M1 (CD86) and M2 (CD206) macrophages surface markers. Flow cytometric analysis was performed to quantify marker expression levels and evaluate the regulatory effects of amino-fullerene on LPS-induced M1 polarization. Three independent experiments were conducted, with a minimum of 20,000 events recorded per sample.

4.13 Enzyme-linked immunosorbent assay (ELISA) assay

Cytokine concentrations were quantified using commercial ELISA

kits according to the manufacturer's protocol. Briefly, samples and standards were added to pre-coated plates, incubated, and washed. Detection antibodies, followed by streptavidin-horseradish peroxidase (HRP) and 3,3',5,5'-tetramethylbenzidine (TMB) substrate, were added. Reactions were stopped with sulfuric acid, and absorbance was measured at 450 nm. Cytokine levels were calculated against the standard curve.

4.14 Crystal violet cell staining

HaCaT cells were treated with gel extract solutions of different concentration gradients for 24 h, then fixed with methanol, stained with 0.1% crystal violet solution (Solarbio, G1064, China) and photographed with a charge-coupled device (CCD) camera.

4.15 Animals and treatment

Male BALB/c mice (6-week-old, wild-type) were obtained from Beijing Huafukang Biotechnology Co., Ltd. (Beijing, China). Animals were maintained under standard Specific Pathogen-free (SPF) conditions with 12/12-h light/dark cycles, and provided with autoclaved water and standard rodent chow ad libitum (Beijing Huafukang Bioscience Co. Inc.). Following experimental procedures, euthanasia was performed by CO₂.

4.16 Hydrogel treatment for psoriasis

Following a 7-day acclimatization period in an SPF environment, the dorsal hair of 6-week-old male BALB/c mice ($n = 6$ per group) was shaved. After normal feeding for 1 day to restore the stratum corneum, all groups except the control were treated with a daily topical application of 62.5 mg of IMQ cream on the shaved dorsal area, followed 6 h later by respective interventions: the Model group received no further treatment; the CB group received 0.1 mL of CB; the TAPC@CB and TPPC@CB groups received 0.1 mL of TAPC@CB and TPPC@CB; and the Daivobet® group received 50 mg/cm² of Daivobet®.

To evaluate recurrence suppression, mice underwent a 15-day recovery after the initial 7-day treatment, followed by a 7-day rechallenge with reduced-dose IMQ (20.8 mg/mouse) at the same lesion site.

During the study, skin thickness was measured with a Vernier caliper, body weight was recorded, and the PASI was assessed (more details are provided in section S3 in the ESM). Lesion tissues were collected post-treatment for histological, molecular, and proteomic analyses.

All animal procedures were approved by the Institutional Animal Care and Use Committee of the Institute of Chemistry, Chinese Academy of Sciences (approval no. SYXK (Jing) 2018-0033).

4.17 Histopathological analysis

The collected tissues were fixed with 4% paraformaldehyde, embedded in paraffin blocks, sectioned, dewaxed with xylene, and rehydrated with an alcohol gradient. For H&E staining, slides were stained with hematoxylin and eosin. For immunohistochemical staining, skin tissue sections were stained with the corresponding antibodies according to the manufacturer's protocol. Sections were scanned using a scanning microscope (KF-PRO-005, KFBIO, China) and analyzed using ImageJ software.

4.18 RNA isolation and RT-qPCR

Total RNA was extracted from lesion tissues using FastPure® Cell/Tissue Total RNA Isolation Kit V2 following the manufacturer's

protocol. Subsequently, 1 μg of total RNA was reverse transcribed into cDNA using the 1st Strand cDNA Synthesis SuperMix (NovoScript, E044-01A) according to the manufacturer's instructions. RT-qPCR was performed in a 20 μL reaction volume using the SYBR One-Step RT-qPCR Kit (NovoScript, E092-01A), following the manufacturer's protocol. The primer sequences are listed in Table S1 in the ESM.

4.19 Western blot assay

HaCaT cells treated with M5, TAPC, and TPPC for 48 h were lysed in Radioimmunoprecipitation assay (RIPA) buffer containing protease and phosphatase inhibitors. Tissue samples were lysed in RIPA buffer containing protease and phosphatase inhibitors using a tissue homogenizer and an ultrasonic homogenizer. Collected proteins were quantified using the bicinchoninic acid (BCA) assay, boiled in 5 $\times$ sample buffer for 10 min, separated by sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE), and transferred to a polyvinylidene fluoride (PVDF) membrane. After blocking with 5% bovine serum albumin (BSA) for 1 h, the membrane was incubated with the primary antibody overnight at 4 °C on a shaking incubator, washed three times with Tris-buffered saline with Tween-20 (TBST), and then incubated with the secondary antibody at room temperature for 1 h. Finally, protein bands were visualized using an enhanced chemiluminescence method (ECL, ABSIN, ABS920).

4.20 RNA-seq

Total RNA was extracted using Trizol (Invitrogen) and quality was verified (RNA integrity number (RIN) > 7.0, 28S:18S ratio > 1.8) using an Agilent 2100 BioAnalyzer and Qubit Fluorometer. Poly(A) mRNA was enriched from 1 μg total RNA using the NEB Next Poly(A) mRNA Magnetic Isolation Module (NEB), followed by fragmentation (~ 200 bp). cDNA libraries were prepared using the NEB Next Ultra RNA Library Prep Kit (NEB) through first- and second-strand cDNA synthesis, end repair, adapter ligation, and PCR amplification. Library quality was assessed using the KAPA Library Quantification kit and Agilent 2100 BioAnalyzer. Paired-end sequencing (150 bp) was performed on an Illumina NovaSeq platform (CapitalBio Technology, Beijing).

4.21 Proteomics

Tissues were homogenized in lysis buffer (8 M urea, 4% 3-[(3-cholamidopropyl)dimethylammonio]propanesulfonate (CHAPS), 20 mM Tris, 30 mM dithiothreitol (DTT)) with protease inhibitors, centrifuged (15,000g, 20 min), and acetone-precipitated. Proteins were reduced (10 mM DTT, 1 h), alkylated (50 mM iodoacetamide, 1 h), and digested with trypsin (1:50, 37 °C, 14 h). Peptides were labeled with 5-mercapto-[1,3,4-thiadiazol-2-ylsulfanyl]-acetic acid (TMT) reagents (1 h), quenched with hydroxylamine, and stored at –80 °C for liquid chromatography-mass spectrometry (LC-MS)/MS analysis.

Peptides were separated using a nano-UPLC system (Thermo Fisher Scientific) with a C18 trap column (3 μm , 75 μm $\times$ 2 cm) and analytical column (2 μm , 75 μm $\times$ 25 cm). Gradient elution was performed at 300 nL/min (3%–30% acetonitrile/0.1% formic acid over 38.5 min). MS analysis used a Q-Exactive mass spectrometer in data-dependent mode: full scans (m/z 350–1600, 70,000 resolution) followed by higher-energy collisional dissociation (HCD)-MS/MS (NCE 29, 3, 500 resolution). Data were acquired using Xcalibur 2.2.

4.22 Bioinformatics analysis

Group-mean matrix (Control/Model/TAPC@CB) was constructed for mfuzz input, while retaining sample-level matrix for statistical testing. Standardize data was standardized and fuzzification parameter m was estimated. Mfuzz clustering was performed ($c = 10$). True members were selected with membership ≥ 0.6 , gene lists were exported for clusters 3/5/9/10. Cluster trend plots were visualized and saved. Differential expression for Model vs. Control and TAPC@CB vs. Model ($\log_2\text{FC}$ and adjusted P -value (P_{adj})) was computed. Proteins were selected with $P_{\text{adj}} \leq 0.05$. Overlap was taken between the two comparisons (299 proteins). Volcano plots and Venn diagrams were visualized. Gene/protein identifiers were harmonized. For each expected cluster, overlap with 299 common DEPs was computed. Consistency of RNA and protein regulation directions were checked. Overlaps with Venn diagrams was visualized. Enrichment analysis (GO/KEGG/Reactome) was performed, using detectable gene/protein sets as background. Significant pathways were reported, visualizing with bar plots. Selection rules: genes belonging to expected clusters with membership ≥ 0.6 ; present in the 299 common DEPs; RNA and protein showing consistent directions.

4.23 Statistical analysis

The statistical significance between groups was obtained through the two-tailed Student's t -test. Multiple comparisons were performed using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test. Data are presented as mean $\pm$ s.e.m. All statistical calculations were conducted using GraphPad Prism software. The significant differences were indicated as follows: $*P < 0.05$, $**P < 0.01$, $***P < 0.001$, and $****P < 0.0001$ versus the control group; $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ and $****P < 0.0001$, versus the model group.

Electronic Supplementary Material: Supplementary material (chemical structures, cell viability, quantification of cell cycle, electron paramagnetic resonance (EPR), quantitation of mean fluorescence intensity (MFI), quantitation of CD86 and CB206, WB, hydrodynamic size, pH values, crystal violet staining, weight changes of mice, epidermal thickness changes of mice, IHC immunostaining, gene expression clusters, volcano plot and functional enrichment analysis, and the primer sequences for the RT-qPCR analysis) is available in the online version of this article at <https://doi.org/10.26599/NR.2026.94908575>.

Data availability

All data needed to support the conclusions in the paper are presented in the manuscript and the Electronic Supplementary Material. Additional data related to this paper may be requested from the corresponding author upon request.

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Declaration of competing interest

The authors declare no competing financial interest.

Author contribution statement

M. H. L.: Investigation, data curation, formal analysis, methodology, writing – original draft, writing – review & editing. B. W. L., W. Z., Y. C. L., Y. T. L., S. L. C., Y. W. P., and Z. H. W.: Investigation, methodology, formal analysis. A. X. C., Y. J. W., J. C. S., Y. X., X. W., J. W. H., and Y. L.: Investigation, methodology. W. H. W.: supervision, funding acquisition, writing – review & editing. J. M. J.: Visualization, supervision, funding acquisition, writing – review & editing. J. L.: Conceptualization, supervision, data curation, funding acquisition, writing – original draft, writing – review & editing. C. R. W. and C. L. B.: Conceptualization, resources, supervision, data curation, funding acquisition, project administration, writing – review & editing.

Informed consent

Not applicable.

Ethics statement

The animal experiments were carried out following the guidelines of the Animal Ethics Committee of the Institute of Chemistry, Chinese Academy of Sciences for the Care and Use of Laboratory Animals and were approved by the Committee on Ethical Use of Animals of the Institute of Chemistry, Chinese Academy of Sciences (Ethical code: ICCAS2024113001).

Use of AI statement

None.

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