PHARMACIA

Pharmacia 73: e205623
DOI 10.3897/pharmacia.73.e205623

Research Article

Celecoxib or diallyl trisulfide topical emulgels, alone or in combination, reduce pruritus and inflammatory cascades in a BALB/c mouse model of imiquimod-induced psoriasis

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Received 26 June 2026 ♦ **Accepted** 23 September 2026 ♦ **Published** 19 October 2026

Citation: Kamel MM, Zaki HF, Saleh RA, Henry SR, Ibrahim MK, Mofreh Bakr M, Abouhussein DMN, Rabie MA (2026) Celecoxib or diallyl trisulfide topical emulgels, alone or in combination, reduce pruritus and inflammatory cascades in a BALB/c mouse model of imiquimod-induced psoriasis. Pharmacia 73: e205623. https://doi.org/10.3897/pharmacia.73.e205623

Abstract

Psoriasis is a chronic, immune-mediated inflammatory skin disease for which no curative treatment currently exists, posing a significant challenge because of its deleterious effects on patients' quality of life and its substantial economic burden on healthcare systems. Current first-line therapies, including corticosteroids and systemic immunosuppressants, are associated with considerable local and systemic side effects, underscoring the need for safer topical alternatives. Topical celecoxib (CXB), a selective cyclooxygenase-2 inhibitor, suppresses prostaglandin-mediated inflammation and pain, whereas diallyl trisulfide (DATS), a naturally derived, slow-releasing hydrogen sulfide donor, has been shown to restore the Th17/Treg balance in other inflammatory disease models. The present study aimed to evaluate the effects of topical application of CXB and DATS emulgels, administered individually and in combination, against imiquimod (IMQ)-induced psoriasis in female BALB/c mice, using clobetasol as a benchmark comparator, and to investigate the underlying mechanisms.

Treatment with CXB, DATS, or their combination significantly relieved pruritus, as demonstrated by reduced scratch bouts, improved Psoriasis Area and Severity Index (PASI) scores, amelioration of histopathological alterations, and restoration of spleen mass. CXB and DATS exerted their antipsoriatic effects by suppressing inflammation, as evidenced by inhibition of the IL-23/IL-22/IL-19/IL-17 axis and reduction of IL-6, JAK2/STAT3 total proteins, along with decreased TNF-α and IFN-γ levels, reduced myeloperoxidase (MPO) content, and diminished serotonin (5-HT) levels. $CD4^+$ and $CD8^+$ T-cell infiltration, assessed by histoscore, was likewise reduced. Across all assessed endpoints, the combination therapy showed encouraging outcomes that warrant direct comparison with clobetasol in future trials. In conclusion, CXB and DATS demonstrated protective effects against IMQ-induced psoriasis by attenuating pruritus and suppressing key inflammatory and immune signaling cascades involving the IL-23/IL-22/IL-19/IL-17 axis and the IL-6/JAK2/STAT3 cascade. These findings support the use of a CXB-DATS emulgel as a promising topical strategy for the treatment of psoriasis.

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PENSOFT

Keywords

celecoxib, diallyl trisulfide, IL-17, IL-23, imiquimod-induced psoriasis, serotonin

Introduction

Psoriasis is a chronic, systemic inflammatory disease characterized by a relapsing-remitting course, significantly impacting patients' quality of life. The prevalence of psoriasis among adults has been steadily rising over time (Huang et al. 2024), increasing the burden of psoriasis treatment (Zhang et al. 2024). Current therapeutic options, including expensive biologics (Colombo et al. 2022), present emerging challenges, such as paradoxical psoriasis reactions associated with tumor necrosis factor (TNF-α) inhibitors and interleukin (IL)-23/IL-17-targeting biologics. These reactions are attributed to disruptions in immune signaling pathways and cytokine recruitment and migration (Orzan et al. 2025). Potential loss of efficacy over time and risks of infections also arise as limitations of biologics (Matwiejuk et al. 2026). Despite the efficacy of biological treatments reflected in better Psoriasis Area and Severity Index (PASI) scores, unrelieved itch remains a prominent complaint (Dickison et al. 2018). Additionally, therapies such as psoralen plus ultraviolet A (PUVA) and cyclosporine have been linked to an elevated risk of skin cancer (Potestio et al. 2024b), while corticosteroids are associated with well-documented adverse effects (Egeberg and Thyssen 2024). These limitations highlight the urgent need for the development of safer, more accessible, and cost-effective treatment alternatives.

Although psoriasis derives from the Greek language, meaning "roughly itching condition" (psora: "itch," sis: "action") (Ravuri 2024), psoriatic itch or pruritus is frequently overlooked despite being reported by approximately 60–90% of psoriatic patients (Komiya et al. 2020). The Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey found itching to be the most important factor contributing to disease severity (Kircik et al. 2024). Moreover, scratching exacerbates psoriasis and can induce new psoriatic lesions in non-lesional areas, a reaction referred to as the Koebner phenomenon (Kalayciyan et al. 2007; Elewski et al. 2019). Psoriatic itch has a more profound and burdensome impact than previously recognized, yet effective therapeutic options remain limited.

Psoriasis can be triggered by psychoneuroimmunological mechanisms, in which neuropeptides and nerve growth factor (NGF) promote keratinocyte (KC) proliferation, T-lymphocyte activation, and vasodilation as well as the Koebner phenomenon (Lugović Mihić et al. 2019). In addition, sensory nerves, particularly C-fibers, produce calcitonin gene-related peptide (CGRP), which further enhances keratinocyte proliferation (Russell et al. 2014). Moreover, neuropeptides recruit and activate granulocytes, macrophages, and monocytes, thereby stimulating the release of prostaglandin E2 (PGE2) and interleukin 10 (IL-10). Concurrently, they promote the secretion of IL-12 and IL-23 by dendritic cells (DCs), which drive T helper (Th)1, Th17, and Th22 subsets to generate immune responses and cause the manifestation of psoriasis (Lugović Mihić et al. 2019; Zhang et al. 2023).

Psoriasis is a multifactorial disease that involves complex interactions among immune cells, primarily Th17 cells, KCs, and DCs, as well as other immune cells, such as Th9, Th22, $CD8^+$ cells, and neutrophils. These cells produce cytokines, including TNF-α, IL-17, and IL-23, leading to perpetual inflammation and KC hyperproliferation (Sieminska et al. 2024). High-throughput analysis (Sieminska et al. 2024) and computational modeling have revealed that cytokines from DCs trigger Th cell differentiation into Th1, Th17, and Th22 subsets, disrupting skin homeostasis and amplifying inflammation through neutrophil activation. In this context, the spleen is critical to the immunological milieu of psoriasis, serving as a primary site of granulopoiesis and promoting neutrophil infiltration in the skin (Shi et al. 2025). Thus, targeting neutrophils alongside inhibition of PGE2 or signal transducer and activator of transcription 3 (STAT3) could represent a potential therapeutic approach for psoriasis (Tsirvouli et al. 2024). Furthermore, Chakith et al. (2025) underscored the significance of targeting cytokine axes involving TNF-α, interferon γ (IFN-γ), IL-23/IL-17A, and IL-22 (Chakith et al. 2025).

Regarding pruritus, mast cell degranulation releases pruritogenic granules containing cytokines, histamine, and serotonin (Nakashima et al. 2019). Serotonin stimulates KC proliferation and upregulates B- and T-lymphocytes, suggesting its potential as a therapeutic target (Huang et al. 2004b). These mediators then interact with specific receptors on axon terminals, activating transient receptor potential vanilloid 1 (TRPV1) channels on sensory nerve fibers (Kim et al. 2024). As part of the transient receptor potential (TRP) channel superfamily, TRPV1 is importantly involved in detecting and transmitting sensory signals, including itch (Shirolkar and Mishra 2022).

Imiquimod (IMQ; Aldara®) is a potent immune response modifier used topically for dermatological conditions such as cutaneous malignancies. However, it has been associated with psoriasis-like side effects. It has triggered flare-ups in patients with psoriasis, leading to the development of the widely used IMQ-induced psoriasiform dermatitis model, first described by van der Fits et al. (2009). In this model, repeated topical

application of IMQ to mouse back skin induces phenotypes that closely resemble human psoriasis (van der Fits et al. 2009; Badanthadka and D'Souza 2020), driven by toll-like receptor 7/8 activation and subsequent inflammatory cytokine release (Hazar-Yavuz et al. 2026). Additionally, IMQ acts as a pruritogen by directly interacting with transient receptor potential ankyrin 1 (TRPA1), inducing itch-like behaviors in both zebrafish larvae and mice (Jakob et al. 2020). In the early stages of psoriasis, an IMQ model showed that nociceptor ablation reduced the proportion of IL-17-producing γδ T cells by disrupting the TRPV1/CGRP/IL-23 axis (Zhang et al. 2021). This model offers the advantage of detecting early events in plaque formation, which is not feasible in human patients (Wohn et al. 2014). Accordingly, it is widely recognized for its simplicity, immunological transparency, and effectiveness in studying psoriasis pathogenesis and evaluating antipsoriatic agents (Badanthadka and D'Souza 2020).

Celecoxib (CXB), a non-steroidal anti-inflammatory drug (NSAID) and selective cyclooxygenase (COX)-2 inhibitor, has shown promise in transdermal formulations because of its enhanced skin permeability and safety profile (Soliman et al. 2011). Localized delivery of CXB enables inhibition of PGE2, a major proinflammatory mediator (Bosch et al. 2022), as well as NGF, which supports inflammation (Woolf et al. 1994; Tellegen et al. 2018). Beyond its anti-inflammatory effects, CXB has been reported to influence immune signaling pathways, including suppression of Janus kinase (JAK)-2 phosphorylation and blockade of IL-6-induced STAT3 activation in hepatocellular carcinoma (Liu et al. 2011). Topical CXB hydrogel has been shown to reduce erythema and inflammatory cytokines, including IL-6 and TNF-α (Shayeganmehr et al. 2023). Accordingly, CXB represents a promising candidate for modulating both inflammatory and immune components in psoriasis.

Despite a case report documenting a bullous eruption induced by oral celecoxib (Aouam et al. 2014), dermal irritation evaluation of a 200 mg nanoemulsion in rabbits showed a primary irritation index of 0, classifying it as non-irritating (Shabrina 2025). While some evidence suggests that NSAIDs could exacerbate psoriasis or increase the risk of psoriatic arthritis (PsA), this relationship is not fully established (Ramírez-Hernández 2025). Modern approaches, such as topical gels, sustained-release tablets, transdermal patches, nanoformulations, and selective COX-2 inhibitors, help reduce systemic side effects while maintaining therapeutic action (Sheikh et al. 2026). Consistent with this localized safety profile, the 2025 French guidelines on systemic treatments for moderate-to-severe psoriasis in adults endorse NSAIDs as adjunctive treatment across all treatment lines for patients presenting with concomitant PsA (Masson Regnault et al. 2026).

Meanwhile, because psoriasis is multifactorial, complementary strategies that address other underlying pathways are warranted. Hydrogen sulfide (H_2S), once considered a toxic pollutant, is now recognized as a vital endogenous gasotransmitter with notable therapeutic potential in various inflammatory dermatological conditions (Wang et al. 2022). Alshorafa et al. (2012) found that serum H_2S levels are lower in patients with psoriasis than in healthy controls, with a negative correlation between H_2S levels and clinical disease severity (Alshorafa et al. 2012). Diallyl trisulfide (DATS), a slow-releasing H_2S donor derived from garlic, has shown greater therapeutic potential than inorganic salts such as sodium hydrosulfide (NaHS) and sodium sulfide (Na_2S), as it mimics the natural, sustained production of H_2S *in vivo* (Hartle and Pluth 2016).

Organosulfur compounds exhibit pronounced anti-inflammatory effects, including suppression of inducible nitric oxide synthase (iNOS) and nitric oxide (NO) production in macrophages (Schepetkin et al. 2019). In a chemical hypoxia-induced HaCaT keratinocyte model, NaHS has been shown to reduce COX-2, PGE2, reactive oxygen species (ROS), IL-1, IL-6, and IL-8 levels (Coavoy-Sánchez et al. 2020), while increasing glutathione (GSH) levels and cell viability (Yang et al. 2011). Moreover, NaHS attenuated TNF-α and IFN-γ expression and reduced neutrophil recruitment in mice with Arthus hypersensitivity responses (Shimizu et al. 2013). Additionally, GYY-4137, a slow-releasing H_2S donor, improved psoriasis symptoms by reducing neutrophil recruitment and pruritus in an IMQ-induced psoriasis model (Schmidt et al. 2015). Conversely, inhibiting endogenous H_2S synthesis aggravated inflammation, as shown by increased neutrophil activity (Rodrigues et al. 2017). Alongside its anti-inflammatory actions, DATS has demonstrated immunomodulatory effects by restoring the balance between Th17 and Treg cells in a murine model of rheumatoid arthritis (Rose et al. 2021). Taken together, current evidence suggests that DATS possesses anti-inflammatory and immunomodulatory actions that may have therapeutic significance in psoriasis. Furthermore, emerging H_2S-NSAID hybrids exhibit much lower toxicity and improved anti-inflammatory effects (Xu et al. 2026).

Accordingly, the present study aimed to investigate the potential ameliorative effects of topical CXB, DATS, or their combination against IMQ-induced psoriasis in BALB/c mice and to delineate their underlying pathways.

Methods

Animals

Fifty-six female BALB/c mice, aged 7–9 weeks and weighing 19–20 g, were obtained from the animal facility at Misr University for Science and Technology (MUST; Giza, Egypt). Female mice were chosen because they develop severe psoriasis in response to imiquimod (Alvarez and Jensen 2016), as well as because of the sex-specific strength of TLR7 responses (Berghöfer et al. 2006; Karnam et al. 2012). The mice

were acclimatized to laboratory conditions for 2 weeks. They were housed in groups of four per stainless-steel cage (30 × 20 × 14 cm^3) under standard conditions: 60 ± 10% humidity, 25 ± 2 °C temperature, and a 12/12-h light/dark cycle. Food and water were provided *ad libitum*. Depilation was performed using Veet® hair removal cream (Pischon et al. 2018) on the rostral area (Sakai et al. 2016), starting 24 hours before the experiment to allow skin recovery from irritation.

Drugs

Aldara® cream: Imiquimod cream 5% (MEDA AB, Sweden).

Vaseline®: Original healing jelly (100% pure petroleum jelly; Unilever, UAE).

Dermovate® topical cream: Clobetasol propionate (CP) 0.05% (SmithKline Beecham, Egypt, under license from GlaxoWellcome Limited, UK).

Emulgel is an effective system for incorporating hydrophobic drugs, enhancing patient acceptability because of its spreadability and greaseless nature (Stanos 2007; Khullar et al. 2012). Natrosol 250 HHR® is used as the gelling agent and oleic acid as the oil phase to improve penetration (Bakr et al. 2020). Emulsion stability is further increased through two surfactants, Cremophor EL and Tween 80, while propylene glycol is included to stabilize the emulsion, boost antimicrobial preservative efficacy, and improve active ingredient delivery through the skin (Binks et al. 2011).

Celecoxib (CXB) emulgel: The preparation of the CXB emulsion followed this protocol: The CXB emulgel was prepared by melting oleic acid (10% w/w) (Fisher Scientific UK, Loughborough, UK) and Cremophor EL® (1% w/w; Sigma-Aldrich, St. Louis, USA) at 70 °C, followed by dissolving CXB (500 µg/0.2 mL) (Kekule Pharma Limited, India) in the molten oil phase with vortex mixing, as described by (Wulff et al. 2010). Simultaneously, a 1% w/v Tween 80 aqueous solution was prepared with propylene glycol (5% w/w), heated to 70 °C, and gradually added dropwise to the oil phase while stirring at 1100 rpm for 15 minutes, followed by homogenization at 15,000 rpm for 5 minutes. Finally, Natrosol 250 HHR® (Ashland Global, Kentucky, USA) (0.75% w/w) was dispersed into the resulting emulsion to form the final emulgel formulation. The CXB dose (500 µg/0.2 mL) was selected because it reduces cutaneous PGE2, MPO activity, and dermal neutrophil infiltration in mouse skin (Wulff et al. 2010).

Plain base (P.B.) emulgel: For comparison, a plain base emulgel (without CXB) was prepared using the same procedure as above and stored at 25 °C.

Diallyl trisulfide (DATS) (≥98% purity by HPLC) was obtained from Sigma-Aldrich (Catalog No. SMB00289, Batch No. SLCD9071). DATS was dissolved in 0.5% w/w dimethylformamide (Fisher Chemical, Germany) and incorporated into the plain base emulgel to achieve a concentration of 25 µmol/0.2 mL; this dose has been shown to exert anti-inflammatory effects by inhibiting COX-2 expression in mouse skin, as described by (Shrotriya et al. 2010).

Combined treatment (tmt.): DATS was incorporated into the CXB emulgel to achieve a concentration of 25 µmol DATS and 500 µg CXB per 0.2 mL. The exact applied dose was 0.2 mL.

Experimental design

Except for the control group, which received a daily topical application of Vaseline®, all mice received a daily topical dose of 62.5 mg of IMQ cream (5%) (Aldara®) on their shaved rostral back and both ears for 10 consecutive days (Kim et al. 2016). On day 8, the mice were randomly assigned by stratified randomization based on body weight to seven different treatment groups (n = 8/group), as follows: Group 1 received Vaseline® followed by the plain base formula and served as the normal control; groups 2–7 received 62.5 mg of IMQ cream (5%), whereas group 2 was left untreated to serve as the IMQ-induced model; meanwhile, group 3 was treated with plain base (P.B.) emulgel; group 4 was treated with clobetasol propionate (CP) (standard group); group 5 was treated with topical CXB emulgel; group 6 was treated with topical DATS emulgel; and group 7 was treated with the combined CXB and DATS emulgel. From day 8 to day 10, treatments were applied 1 h after the application of either IMQ or Vaseline®. From day 11 through day 14, IMQ and Vaseline® applications were discontinued, and only treatment applications continued. In accordance with the ARRIVE 2.0 guidelines, outcome assessments were performed under blinded conditions.

Exclusion criteria: Appearance of any signs of cutaneous injury after hair removal using depilatory cream that may affect research outcomes.

Severity scoring of skin inflammation

The severity of psoriatic lesions was assessed daily using a modified clinical PASI score, following the methodology outlined by Wu et al. (2019). Erythema, scaling, and skin thickness were scored individually on a scale of 0 to 4, where 0 represented absence, 1 indicated mild severity, 2 denoted moderate severity, 3 signified pronounced severity, and 4 indicated highly pronounced severity. The total score for these three parameters, ranging from 0 to 12, served as an indicator of inflammation severity (Wu et al. 2019); days 1, 6, 8, 10, and 14 were the chosen time points for statistical analysis.

Itch assessment

To count scratch bouts, mice were individually placed in cages for habituation twice (60 min each) at 48 h and 24 h before videotaping began. On day 15 (22–24 h after the last topical application), mice were videotaped from above for 30 min (Kodji et al. 2019). A scratch bout was described as one or more rapid backward and forward movements of the hind paw directed only toward the treated area, followed by toe licking or biting or the hind paw landing on the floor (Sakai et al. 2016).

After videotaping (day 15), mice were anesthetized with thiopental (40 mg/kg, i.p.) (Flecknell 2009), and blood samples were collected via the retro-orbital plexus. The collected blood was centrifuged at 1000 rpm for 15 min, and the sera were aliquoted into four subsets (n = 5 per subset) and stored at −80 °C for later analysis of cytokines, including IL-6, IL-17, IFN-γ, and TNF-α.

Following blood collection, mice were euthanized using sodium pentobarbital (100 mg/kg, i.p.) (Van Tassell et al. 2010). Left ear tissues were excised, and skin samples were taken from the rostral back area. These skin samples were cut into two rectangular pieces (Silva et al. 2014). One piece was fixed in 10% neutral buffered formalin for histological and immunohistochemical examination (n = 4/group), with six sections/animal and three fields/section; thus, 18 microscopic fields were evaluated per animal. Meanwhile, the other skin sample pieces (n = 5/group) were homogenized in PBS to determine IL-23, IL-22, IL-19, and serotonin levels.

The ear tissues were stored at −80 °C and later divided into two subsets (n = 4 per subset) for further analysis, comprising a myeloperoxidase (MPO) assay and western blot analysis. Finally, spleens were harvested, weighed, and recorded as spleen mass (Jabeen et al. 2020) and then kept in 10% neutral buffered formalin.

Biochemical parameters

Enzyme-linked immunosorbent assay (ELISA)

MyBioSource mouse ELISA kits (CA, USA) were utilized to assess MPO (Catalog No. MBS700747), IL-6 (Catalog No. MBS824703), IL-17 (Catalog No. MBS175940), IL-22 (Catalog No. MBS8291422), TNF-α (Catalog No. MBS825075), IL-19 (Catalog No. MBS2516094), and serotonin (Catalog No. MBS723181), whereas CUSABIO mouse ELISA kits (TX, USA) were used to determine IFN-γ (Catalog No. CSB-E04578m) and IL-23 (Catalog No. E0519Mo). All procedures were performed according to the manufacturers' instructions.

Western blot analysis

Ears (Zhu et al. 2021) were treated with RIPA lysis buffer (Catalog No. PL005, Bio BASIC Inc., Markham, ON, Canada), and protein concentration was determined using the Bradford Protein Assay Kit (Catalog No. SK3041, BIO BASIC Inc.). A total of 20 μg of protein per sample was denatured and loaded onto a polyacrylamide gel prepared with the TGX Stain-Free™ FastCast™ Acrylamide Kit (Catalog No. 1610181, Bio-Rad Laboratories, CA, USA). Proteins were separated using an SDS-PAGE buffer (25 mM Tris base, 190 mM glycine, 0.1% SDS, pH 8.3), with 20 μg of protein loaded per well, and a molecular weight marker (Catalog No. PM008-0500, BLUelf pre-stained protein ladder, GeneDireX, Taiwan) was included. The gel was run at 50 V for 20 min, followed by 100–150 V for 1 h, and then visualized using stain-free technology with a ChemiDoc™ imager (Bio-Rad, USA). Proteins were transferred using Bio-Rad's Trans-Blot Turbo system at 25 V for 7 min in transfer buffer (25 mM Tris, 190 mM glycine, 20% methanol, pH 8.3). The membrane was blocked in buffer (20 mM Tris, pH 7.5, 150 mM NaCl, 0.1% Tween 20, 3% BSA) and incubated overnight at 4 °C with primary monoclonal antibodies (Thermo Fisher, MA, USA) against JAK2 (Catalog No. AHO1352) and STAT3 (Catalog No. AHO1282). After washing with TBST, an HRP-conjugated secondary antibody (Novus Biologicals) was applied for 1 h at room temperature, followed by chemiluminescent detection using Clarity™ Western ECL substrate (Bio-Rad). Signals were captured using a CCD camera-based ChemiDoc™ MP imager, and the relative band intensity of the target proteins was quantified against control samples using beta-actin for normalization, as described by (Jovčevska et al. 2014).

Histopathological examination

Tissues were collected and fixed in 10% neutral buffered formaldehyde for 24 h to stabilize and fix tissue proteins. Dehydration, clearing, paraffin infiltration, and embedding were performed; wax blocks were then sectioned with a microtome into 5 μm sections and stained with hematoxylin and eosin according to (Suvarna et al. 2019).

Epidermal thickness was measured as follows: 66 measurements were performed for each mouse from three random areas between hair follicles, spaced 10 μm apart, where the distance between the basal membrane and the upper surface of the stratum granulosum was considered the epidermal thickness according to the method described by (Pischon et al. 2018), using ImageJ 1.50i software.

Spleen description was performed according to Haley et al. (2005). Additionally, Baker's scoring system was used to assess pathological alterations on a scale from 0 to 10 (Luo et al. 2016).

Immuno-histochemical determination of mouse skin $CD4^+$ and $CD8^+$

Abcam anti-CD4 antibody (Catalog No. ab183685) and Novus Biologicals CD8 antibody (Catalog No. NBP2-29475) were used to detect $CD4^+$ and $CD8^+$ antigens, respectively. The principle relies on specific antibody-antigen recognition, visualized by a color change from antibodies conjugated to an enzyme, such as peroxidase, which initiates a chemical reaction (Wang and Lebrec 2017). Images were captured using a Euromex digital camera at 200 × magnification and analyzed with Fiji 1.53f51 software (Schindelin et al. 2012) using the IHC Profiler plugin, as outlined by (Varghese et al. 2014). Staining intensity was evaluated using the weighted histoscore (H-score) method, which combines the percentage of cells staining at different intensities (weak, moderate, and strong) to produce a score between 0 and 300. This semiquantitative method is well established for tissue analysis, as reported by Ahmad et al. (2011).

Sample size

Sample size was calculated *a priori* using G*Power software v. 3.1.9.7 for one-way ANOVA among seven experimental groups. Anticipating pronounced differences in PASI scores between model and treatment cohorts, a large effect size ($f = 0.55$, based on Cohen's guidelines) was specified. With the significance level set at $\alpha = 0.05$ and power $(1 - \beta)$ at 0.80, a total sample size of 56 ($n = 8$ per group) was required to detect significant treatment effects.

Statistical analysis

Normality was assessed prior to comparisons between groups using the Shapiro–Wilk and Kolmogorov–Smirnov tests. For parametric data involving a single variable, a one-way ANOVA followed by Tukey's multiple comparisons test was applied, with results presented as mean ± SD. For non-parametric data, the Kruskal–Wallis test followed by Dunn's post hoc test was used, and data were reported as median (min–max). In cases involving multiple variables, such as the modified PASI score, a two-way repeated-measures ANOVA followed by Sidak's post hoc test was conducted to assess the effects of both time and treatment. To evaluate the relationship between the observed changes in inflammatory and signaling protein levels and disease severity (PASI score and number of scratch bouts/30 min), Pearson correlation analysis was performed. The correlation coefficient is a statistical measure often used to show an association between variables; the coefficient ranges from −1 to +1 (Janse et al. 2021). An absolute magnitude from 0.00 to 0.10 indicates negligible correlation, 0.10 to 0.39 denotes weak correlation, 0.40 to 0.69 signifies moderate correlation, 0.70 to 0.89 indicates strong correlation, and 0.90 to 1.00 represents very strong correlation (Schober et al. 2018). All analyses were conducted using Prism software v. 10 (GraphPad, California, USA), and a significance level of $p \leq 0.05$ was considered. The Bliss Independence Model (Zhao et al. 2014) was used to predict the combined effect of CXB and DATS. The method compares the observed combination response (Y_O) with the predicted combination response (Y_P). Typically, the combination effect is declared synergistic if Y_O is greater than Y_P.

Y_p can be predicted using the complete additivity of probability theory as,

$$Y_p = Y_a + Y_b - (Y_a \times Y_b)$$

Results

In the statistical analysis, no significant difference was detected between the IMQ group (group 2) and the P.B. group (group 3), except for the modified PASI score and the number of scratch bouts, due to the emollient effect of the plain base. Consequently, the comparison focused solely on the IMQ group.

The Bliss Independence Model results did not support additivity or synergy, except for IL-23, for which the combined treatment showed a synergistic effect.

Effect of topical CXB and DATS emulgels, *per se* or in combination, on modified PASI score in IMQ-induced psoriasis-like symptoms in female BALB/c mice

Topical application of IMQ cream for 10 consecutive days significantly worsened the cumulative PASI score to 4.6 (95% CI 3.366–5.884) (Fig. 1), compared with the control group, which maintained a score of 0. Conversely, topical application of P.B. reduced the PASI score to 2.37 ($p = 0.0093$; 95% CI 1.609–3.141), and treatment with CXB, DATS, or their combination showed notable improvement in the cumulative PASI score. Specifically, CXB reduced the score to 1.75 (95% CI 0.6784–2.822), DATS to 1.4 (95% CI 0.4883–2.262), and the combined treat-

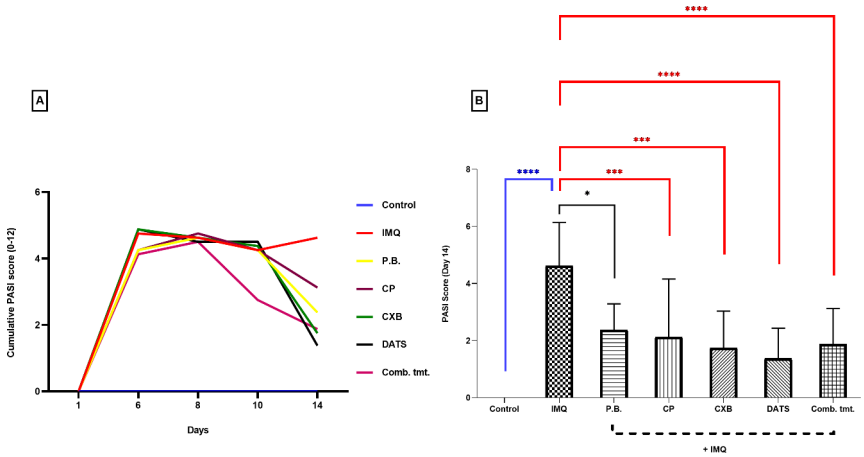

Figure 1. Modified PASI score of topical CXB and DATS emulgels, *per se* or in combination, against IMQ-induced psoriasis in female BALB/c mice. **A.** Cumulative PASI score throughout the experiment. The cumulative PASI score was calculated daily by adding the scores obtained for erythema, skin scaling, and thickening, and results were expressed as the mean ($n = 8$), using two-way repeated-measures ANOVA followed by Sidak's post hoc test; **B.** Cumulative score on day 14. Results were expressed as mean ± SD ($n = 8$/group), using one-way ANOVA followed by Tukey's multiple comparisons test. *$p < 0.05$, ***$p < 0.001$, ****$p < 0.0001$. Effect size ($R^2 = 0.5323$). CXB: celecoxib; DATS: diallyl trisulfide; IMQ: imiquimod; PASI: Psoriasis Area and Severity Index; P.B.: plain base.

ment to 1.9 (95% CI 0.8330–2.917), all showing significant amelioration compared with the IMQ-treated group. Moreover, these treatments, either individually or in combination, were comparable to the standard treatment, with no statistically significant differences compared with CP.

Effect of topical CXB and DATS, *per se* or in combination, on itch assessment (number of scratch bouts/30 min) and skin serotonin in IMQ-induced psoriasis in female BALB/c mice

Topical IMQ application elicited pronounced scratching behavior, as shown by a 3.7-fold increase in scratch bouts per 30 min (95% CI 95.59–134.4). Likewise, it increased serotonin levels 2.8-fold compared with the control group. However, P.B. decreased the number of scratch bouts by 45% (95% CI 37.07–88.68), and treatment with CXB, DATS, or their combination diminished scratch bouts by 66% (95% CI 26.72–51.78), 77% (95% CI 15.81–37.44), and 70% (95% CI 21.59–46.66), respectively, and serotonin content by 44%, 44%, and 56%, respectively, compared with the IMQ group. Interestingly, both individual treatments and the combination were comparable to the standard treatment, with no significant differences; however, the combined treatment was superior to the standard treatment in reducing serotonin levels by 23% (Fig. 2).

Effect of topical CXB and DATS emulgels, alone or in combination, on spleen histological architecture and absolute spleen weight in IMQ-induced psoriasis in female BALB/c mice

As depicted in Fig. 3, the splenic tissues of the control group (A) exhibited normal histological architecture, characterized by a thin capsule, delicate trabeculae, and a well-organized reticular network containing large polygonal megakaryocytes. The parenchyma displayed scattered white pulp with central arterioles surrounded by lymphocytes and red pulp composed of splenic cords and blood-filled sinusoids.

In contrast, the IMQ and P.B. groups (B and C) showed significant architectural disruption. These included a marked increase in the size and number of periarteriolar lymphoid sheaths (PALS), with dense lymphocytic infiltration and prominent lymphoid follicles accompanied by an enlarged marginal zone. The red pulp was notably reduced in size, lymphocyte density, and hematopoietic cell content. Additionally, there was a noticeable increase in tingible body macrophages, megakaryocytes, pigmented macrophages, and aggregated macrophages.

The CP (D) and DATS (F) groups showed partial restoration of splenic architecture, with reduced size, number, and lymphocytic content in the PALS, marginal zone, and lymphoid follicles. The red pulp also appeared reduced, though there was a mild increase in macrophage aggregates and megakaryocytes. Interestingly, the CXB group (E) exhibited only minimal to mild increases in the size and cellularity of the PALS and lymphoid follicles, which remained within the boundaries of a relatively normal marginal zone. The red pulp, however, was reduced in lymphocytes and hematopoietic elements, with a mild increase in tingible body macrophages, megakaryocytes, pigmented macrophages, and macrophage aggregates. Notably, the combined treatment group (G) preserved near-normal splenic architecture. The PALS, marginal zone, and lymphoid follicles were largely maintained, with only minimal increases in lymphoid follicle size. The red pulp showed a slight reduction in lymphocytes and hematopoietic cells, along with a mild increase in apoptotic cells.

In parallel, topical IMQ cream caused a significant 88% increase in absolute spleen weight compared with the control group. In contrast, topical treatment with CXB, DATS, or their combination reduced absolute spleen weight by

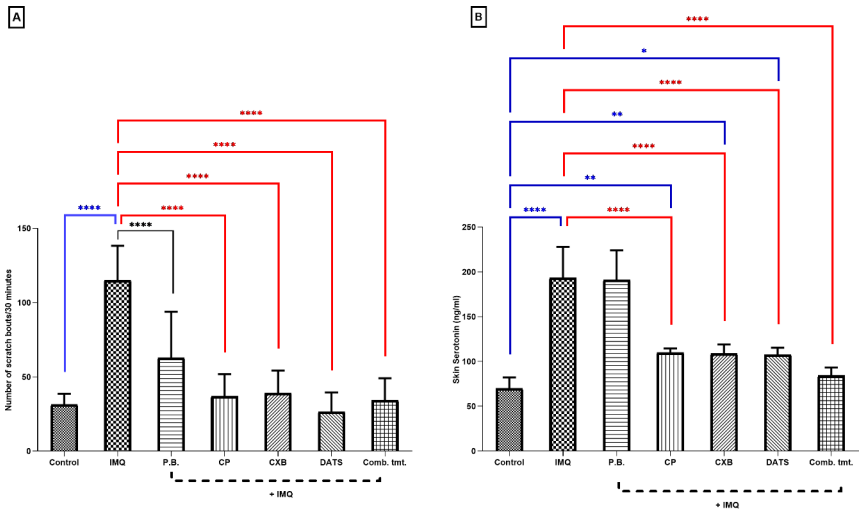

Figure 2. Effect of topical CXB and DATS emulgels, *per se* or in combination, on **A.** Number of scratch bouts/30 min and **B.** Skin serotonin content in IMQ-induced psoriasis in female BALB/c mice. Data were expressed as mean ± SD (n = 8/group for scratch bout count and n = 5/group for serotonin), using one-way ANOVA followed by Tukey's multiple comparisons test. *$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$. **A.** Number of scratch bouts/30 min (R^2 = 0.7365); **B.** Skin serotonin content (R^2 = 0.8696). CXB: celecoxib; DATS: diallyl trisulfide; IMQ: imiquimod; P.B.: plain base.

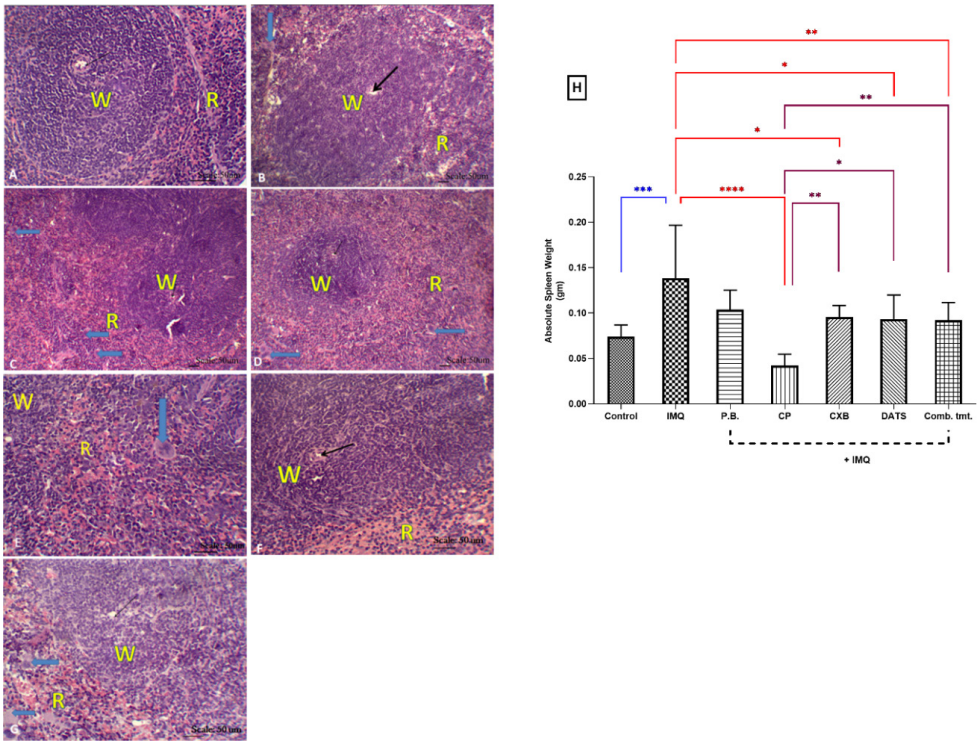

Figure 3. Absolute spleen weight of topical CXB and DATS emulgels, *per se* or in combination, against IMQ-induced psoriasis in female BALB/c mice. Photomicrographs (H&E stain) of splenic tissues demonstrated **A.** Control group; **B.** IMQ group; **C.** IMQ + P.B.; **D.** IMQ + CP; **E.** IMQ + CXB; **F.** IMQ + DATS; and **G.** IMQ + combined tmt. **H.** Absolute spleen weight. R: red pulp; W: white pulp; black arrow: central arteriole; blue thick arrow: megakaryocytes. Data were expressed as mean ± SD (n = 8/group), using one-way ANOVA followed by Tukey's multiple comparisons test. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001. (R^2 = 0.4998). CXB: celecoxib; DATS: diallyl trisulfide; IMQ: imiquimod; tmt.: treatment. Scale bar: 50 μm.

31% (p = 0.0272), 33% (p = 0.0241), and 33% (p = 0.0033), respectively, relative to the IMQ group. Notably, the CP group exhibited the least reduction in absolute spleen weight among the treatment groups (Fig. 3H).

Effect of topical CXB and DATS emulgels, alone or in combination, on skin histological architecture and epidermal thickness in IMQ-induced psoriasis in female BALB/c mice

As depicted in Fig. 4 and summarized in Table 1, the skin of the control group (Fig. 4A) exhibited normal architecture with no abnormalities. In contrast, the IMQ and IMQ + P.B. groups (Fig. 4B, C) displayed several pathological changes, including moderate hyperkeratosis, focal parakeratosis, and acanthosis, with single rete ridge formations, focal Munro abscesses, vacuolar degeneration of the stratum spinosum and basal layers, and disappearance of the stratum granulosum in several areas. Additional findings included moderate perivascular lymphocytic infiltration, angiotelectasis, mild intradermal edema, and alterations in sebaceous glands. The IMQ + CP group (Fig. 4D) showed moderate hyperkeratosis, an atrophied prickle cell layer, preserved stratum granulosum in many areas, no rete ridges or Munro abscesses, and atrophic sebaceous glands and hair follicles. The IMQ + CXB group (Fig. 4E) revealed mild hyperkeratosis, focal acanthosis, rare rete ridges, focal disappearance of the stratum granulosum, and cytoplasmic vacuolar degeneration in the basal layer, with no intradermal edema. The IMQ + DATS group (Fig. 4F) demonstrated mild hyperkeratosis and focal acanthosis, with well-preserved prickle cell layers and sebaceous gland structures. Only rare cytoplasmic degeneration was observed. Finally, the IMQ + combined treatment group (Fig. 4G) showed the most favorable outcomes, with minimal pathological changes. This group demonstrated mild hyperkeratosis, rare acanthosis, and rare rete ridge formations. There was minimal basal layer degeneration, no evidence of edema, and normal blood vessel and sebaceous gland structures.

Similarly, topical IMQ cream significantly increased epidermal thickness, showing a 2.8-fold rise compared with the control group. Conversely, treatment with CXB, DATS, or their combination reduced epidermal thickness by 56%, 54%, and 55%, respectively, relative to the IMQ group. Notably, the CP group showed the most pronounced decrease in epidermal thickness among all groups (Fig. 4H).

Effect of topical CXB and DATS emulgels, *per se* or in combination, on IL-23, IL-22, IL-19, and IL-17 in IMQ-induced psoriasis in female BALB/c mice

In the same context, topical IMQ significantly increased proinflammatory cytokine production, worsening the

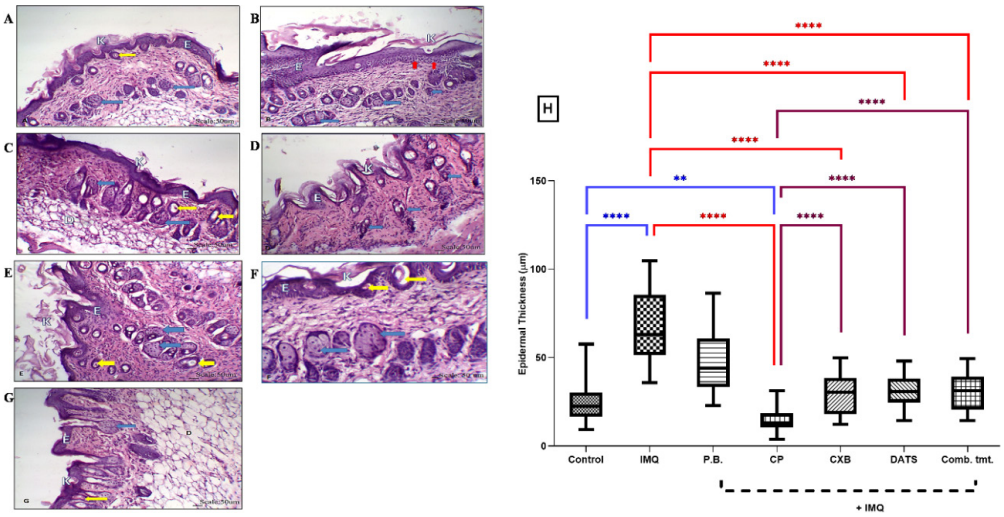

Figure 4. Epidermal thickness of topical CXB and DATS emulgels, *per se* or in combination, against IMQ-induced psoriasis in female BALB/c mice. Photomicrographs (H&E stain) of skin tissue represented **A.** Control group; **B.** IMQ group; **C.** IMQ + P.B.; **D.** IMQ + CP; **E.** IMQ + CXB; **F.** IMQ + DATS; and **G.** IMQ + combined tmt. **H.** Epidermal thickness (µm). K: stratum corneum; E: epidermis; red arrow: stratum basale; blue arrow: sebaceous gland; yellow arrow: hair follicles; D: dermis. Results were presented as median (min–max) (n = 4/group), using the Kruskal–Wallis test followed by Dunn's post hoc test. $^{**}p < 0.01$, $^{****}p < 0.0001$. CXB: celecoxib; DATS: diallyl trisulfide; IMQ: imiquimod; tmt.: treatment. Scale bar: 50 µm.

Table 1. Pathological scores based on Baker's scoring system (M [IQR]).

		Pathological scores based on Baker's scoring system (M[IQR])							
	Items	**Score**	**Control**	**IMQ**	**IMQ + P.B.**	**IMQ + CP**	**IMQ + CXB**	**IMQ + DATS**	**IMQ + Comb. tmt.**
keratin	Munro abscess	2.0	0 (0)	2 (0)	2 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Hyperkeratosis	0.5 (0)	0 (0)	0.5 (0)	0.5 (0.375)	0.5 (0.5)	0.5 (0)	0.5 (0)	0.5 (0.375)
	Parakeratosis	1.0 (0)	0 (0)	1 (0)	1 (0)	0 (0.5)	0 (0)	0 (0)	0 (0)
Epidermis	Thinning above papillae	0.5 (0)	0 (0)	0.5 (0)	0.5 (0)	0 (0)	0 (0)	0.5 (0)	0 (0)
	Lengthening and clubbing of rete ridges	1.5 (0)	0 (0)	1.5 (0)	1.5 (0)	0 (0)	1.5 (0)	0 (0)	0.5 (0)
	Acanthosis	0.5 (0)	0 (0)	0.5 (0)	0.5 (0)	0 (0)	0 (0)	0.5 (0)	0 (0)
	Lack of granular layer	1.0	0 (0)	1 (0)	1 (0)	0.5 (0)	0.5 (0)	0 (0)	0 (0)
Dermis	Lymphocytic infiltration								
	Mild	0.5	0 (0.5)	0 (0)	0 (0)	0.5 (0)	0 (0)	0.5 (0)	0 (0.375)
	Moderate	1.0	0 (0)	1 (1)	1 (0)	0 (0)	1 (0)	0 (0)	0 (0)
	Marked	2.0	0 (0)	0 (1.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Papillary congestion	0.5 (0)	0 (0)	0.5 (0)	0.5 (0)	0.5 (0.375)	0.5 (0)	0 (0)	0 (0)
Total score			0 (0.5)	8.5 (1.5) ****a	8.5 (0.3750) ****a	2 (1.375) *b	4 (0)	2 (0)	1 (0.75) ***b

Table format adapted from the Bakers scoring system parameters outlined by (Luo et al. 2016). Pathological scores of topical CXB and DATS, *per se* or in combination, against IMQ-induced psoriasis in female BALB/c mice. Results were presented as median (M) and the interquartile range [IQR], using the Kruskal–Wallis test followed by Dunn's post hoc test. a. Compared with the control group. b. Compared with the IMQ group. c. Compared with IMQ + CP. $^{*}p < 0.05$, $^{***}p < 0.001$, $^{****}p < 0.0001$. CP: clobetasol propionate; CXB: celecoxib; DATS: diallyl trisulfide; IMQ: imiquimod; P.B.: plain base.

inflammatory response. Specifically, the IMQ group showed notable elevations in lesional skin IL-23 (1.9-fold), IL-22 (3.6-fold), and IL-19 (2.2-fold), as well as serum IL-17 (3.9-fold), compared with the control group. In contrast, treatment with CXB, DATS, or their combination attenuated the inflammatory response. It reduced IL-23 levels by 23% (p = 0.0058), 18% (p = 0.0491), and 42%, respectively; IL-22 levels by 57%, 54%, and 70%, respectively; IL-19 levels by 38%, 41%, and 51%, respectively; and IL-17 levels by 52%, 52%, and 68%, respectively, compared with the IMQ group. Notably, the combined treatment produced a greater reduction in IL-17 levels than both the standard and individual treatments. For IL-23, individual and combined treatments yielded results similar to the standard treatment, with no significant difference, although the combined treatment produced a greater decrease in IL-23 levels than the individual treatments. Using the Bliss Independence Model, Y_P = 0.23 + 0.18 – (0.23 * 0.18) = 0.3686, Y_O = 0.42, since $Y_O > Y_P$, the combined treatment had synergistic effects. For IL-22, the individual treatments were similar to the standard, with no significant difference. Still, the combined treatment showed a greater reduction in IL-22 and IL-19 levels of 35% (p = 0.0444) and 28%, respectively, compared with the standard treatment (Fig. 5).

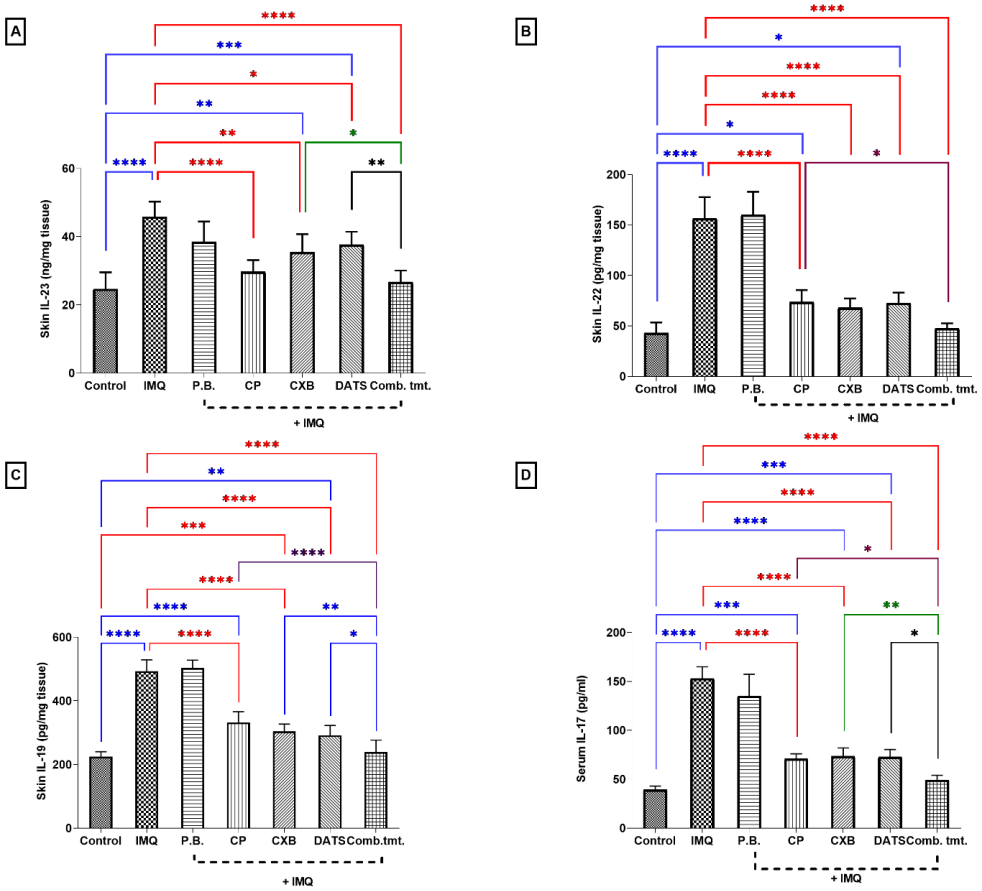

Figure 5. Effect of topical CXB and DATS emulgels, *per se* or in combination, on **A.** Skin IL-23; **B.** Skin IL-22 content; **C.** Skin IL-19; and **D.** Serum IL-17 levels in IMQ-induced psoriasis in female BALB/c mice. Data were expressed as mean ± SD (n = 5/group) and analyzed by one-way ANOVA followed by Tukey's multiple comparisons test. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001. For IL-23 (R^2 = 0.7385). For IL-22 (R^2 = 0.9234). For IL-19 (R^2 = 0.9398). For IL-17 (R^2 = 0.9399). CXB: celecoxib; DATS: diallyl trisulfide; IMQ: imiquimod; IL-23: interleukin 23; IL-22: interleukin 22; IL-19: interleukin 19; IL-17: interleukin 17.

Effect of topical CXB and DATS emulgels, *per se* or in combination, on IL-6, JAK2, and STAT3 in IMQ-induced psoriasis in female BALB/c mice

As illustrated in Fig. 6, topical IMQ application provoked an inflammatory cascade, evidenced by increased serum IL-6 levels and total ear JAK2 and STAT3 protein expression, which increased by 4.9-, 5.3-, and 6.9-fold, respectively, relative to the control group. Conversely, treatment with CXB, DATS, or their combination successfully mitigated the inflammatory reaction and decreased IL-6 levels by 49%, 50%, and 68%, respectively; JAK2 protein expression by 49%, 46%, and 64%, respectively; and STAT3 protein expression by 56%, 54%, and 71%, respectively, compared with the IMQ group. Notably, the combined treatment substantially decreased IL-6 levels and JAK2 and STAT3 protein expression compared with the standard treatment by 40% (p = 0.0049), 26%, and 37% (p = 0.0012), respectively. Furthermore, the combined treatment reduced JAK2 protein expression to levels comparable to those of the standard and CXB treatments, with no significant differences. However, it was significantly more effective than DATS alone by 34% (p = 0.0431), demonstrating a remarkable improvement.

Effect of topical CXB and DATS emulgels, *per se* or in combination, on IFN-γ, TNF-α, and MPO in IMQ-induced psoriasis in female BALB/c mice

To further verify its inflammatory effect, topical IMQ application triggered a positive feed-forward inflammatory loop, as evidenced by increases in the inflammatory cytokines IFN-γ and TNF-α and the MPO enzyme, which were elevated 2.5-, 3.8-, and 2.3-fold, respectively, compared with the control group. However, treatment with CXB, DATS, or their combination attenuated the inflammatory loop. It reduced IFN-γ levels (36%, 37%, and 51%, respectively), TNF-α levels (53%, 53%, and 64%, respectively), and MPO content (37%, 38%, and 50%, respectively), compared with the IMQ group. Interestingly, both individual treatments and the combination were comparable to the standard treatment, with no significant differences noted in TNF-α and MPO. However, the combined treatment proved superior to the standard treatment in reducing IFN-γ levels by 21% (p = 0.0062) (Fig. 7).

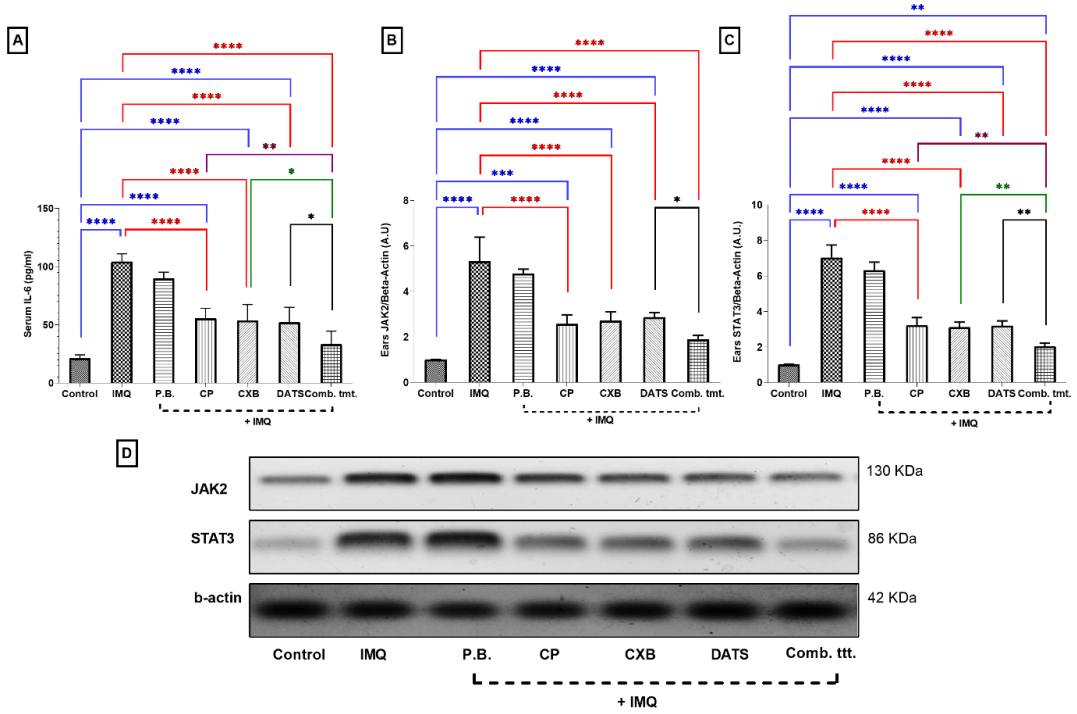

Figure 6. Effect of topical CXB and DATS emulgels, *per se* or in combination, on **A.** Serum IL-6 levels, as well as ear protein expression of **B.** JAK2 and **C.** STAT3, against IMQ-induced psoriasis in female BALB/c mice. **D.** Western blot bands of JAK2 and STAT3 protein expression. Data were expressed as mean ± SD (n = 4/group for JAK2 and STAT3 and n = 5/group for IL-6), using one-way ANOVA followed by Tukey's multiple comparisons test. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. For IL-6 ($R^2 = 0.9055$). For JAK2 ($R^2 = 0.9175$). For STAT3 ($R^2 = 0.9701$). CXB: celecoxib; DATS: diallyl trisulfide; IMQ: imiquimod; JAK2: Janus kinase 2; STAT3: signal transducer and activator of transcription 3; IL-6: interleukin 6.

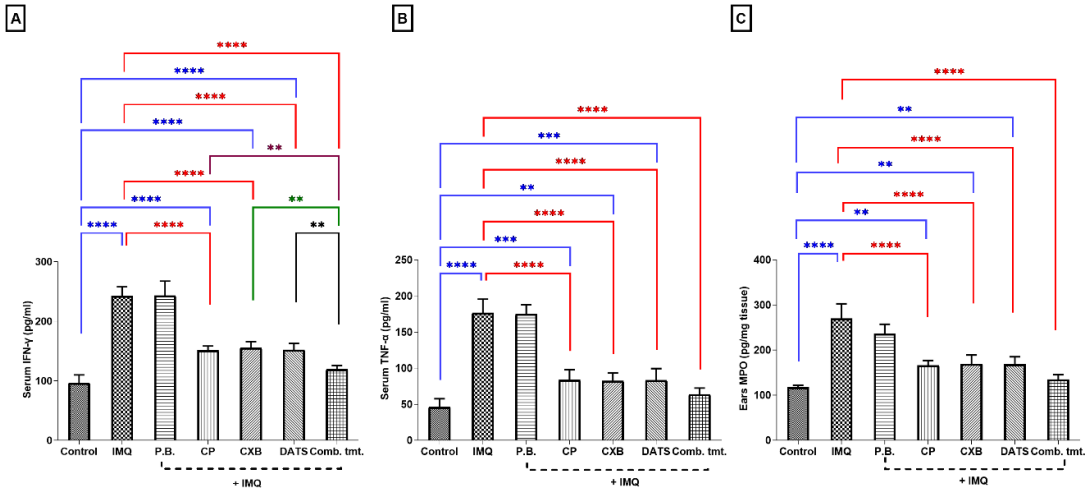

Figure 7. Effect of topical CXB and DATS emulgels, *per se* or in combination, on serum **A.** IFN-γ and **B.** TNF-α levels, as well as **C.** Ear MPO content, against IMQ-induced psoriasis in female BALB/c mice. Data were expressed as mean ± SD (n = 4/group for MPO and n = 5/group for IFN-γ and TNF-α), using one-way ANOVA followed by Tukey's multiple comparisons test. **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. For IFN-γ ($R^2 = 0.9453$). For TNF-α ($R^2 = 0.9379$). For MPO ($R^2 = 0.9009$). CXB: celecoxib; DATS: diallyl trisulfide; IMQ: imiquimod; IFN-γ: interferon-gamma; TNF-α: tumor necrosis factor-alpha; MPO: myeloperoxidase.

Effect of topical CXB and DATS emulgels, *per se* or in combination, on skin CD4⁺ immunohistochemistry in IMQ-induced psoriasis in female BALB/c mice

As illustrated in Fig. 8H, IMQ-treated mice exhibited an 84% increase in CD4⁺ histoscore compared with the control group. However, treatment with CXB, DATS, or their combination significantly reduced the CD4⁺ histoscore by 41%, 38%, and 46%, respectively, relative to the IMQ-treated mice. Furthermore, these treatments, whether administered individually or in combination, showed efficacy comparable to the standard treatment, with no statistically significant differences compared with CP.

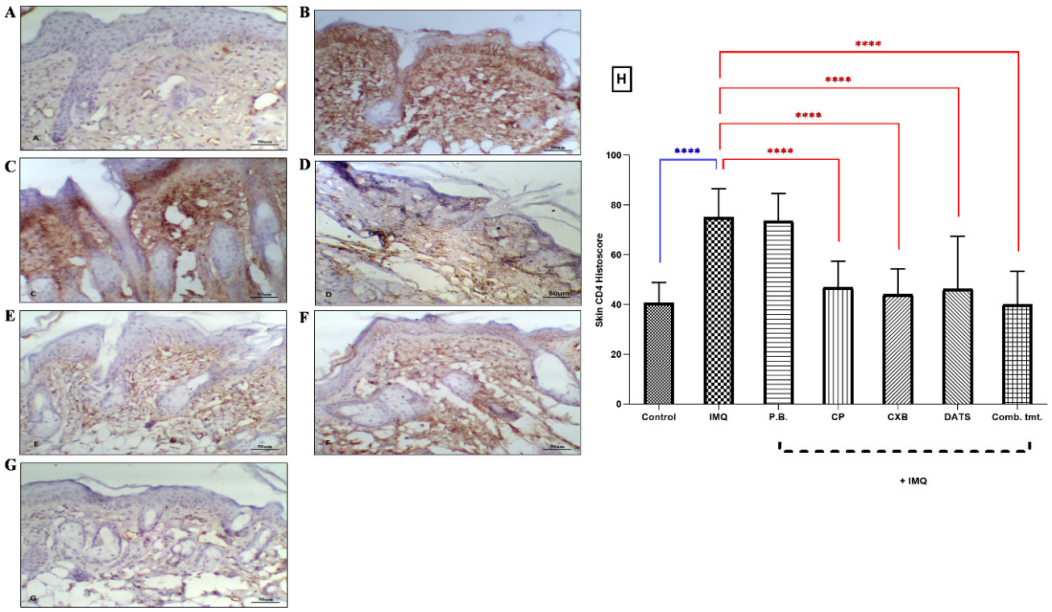

Figure 8. Effect of topical CXB and DATS emulgels, *per se* or in combination, on immunohistochemical analysis of skin CD4⁺ staining against IMQ-induced psoriasis in female BALB/c mice. Photomicrographs showed immunohistochemical staining of skin CD4⁺ from **A.** Control group; **B.** IMQ group; **C.** IMQ + P.B.; **D.** IMQ + CP; **E.** IMQ + CXB; **F.** IMQ + DATS; and **G.** IMQ + combined tmt. **H.** Skin CD4⁺ histoscore. Data were expressed as mean ± SD (n = 4/group), using one-way ANOVA followed by Tukey's multiple comparisons test. ****$p < 0.0001$. ($R^2 = 0.5652$). CXB: celecoxib; DATS: diallyl trisulfide; IMQ: imiquimod; CD4⁺: cluster of differentiation 4; tmt.: treatment. Scale bar: 50 µm.

Effect of topical CXB and DATS emulgels, *per se* or in combination, on skin CD8⁺ immunohistochemistry in IMQ-induced psoriasis in female BALB/c mice

Topical IMQ application increased the CD8⁺ histoscore by 62% compared with the control group. In contrast, treatment with CXB, DATS, or their combination reduced the CD8⁺ histoscore by 27% (p = 0.0116), 30% (p = 0.0060), and 30% (p = 0.0036), respectively, relative to the IMQ group. Notably, these treatments, whether administered alone or in combination, yielded results similar to the standard treatment, CP, with no statistically significant differences between them (Fig. 9H).

Table 2. Correlation between inflammatory cytokines, signaling proteins, and disease severity (PASI).

	PASI cumulative day 14 vs. skin IL-23	PASI cumulative day 14 vs. skin IL-22	PASI cumulative day 14 vs. skin IL-19	PASI cumulative day 14 vs. serum IL-17	PASI cumulative day 14 vs. serum IL-6	PASI cumulative day 14 vs. ears JAK2	PASI cumulative day 14 vs. ears STAT3	PASI cumulative day 14 vs. serum IFN-γ	PASI cumulative day 14 vs. serum TNF-α	PASI cumulative day 14 vs. ears MPO
Pearson *r*	0.7901	0.7728	0.7909	0.8495	0.8787	0.8641	0.8630	0.8144	0.8108	0.8782
95% confidence interval	0.09145–0.9675	0.04717–0.9645	0.09345–0.9676	0.2677–0.9773	0.3715–0.9820	0.3178–0.9797	0.3139–0.9795	0.1585–0.9716	0.1482–0.9710	0.3696–0.9819
R squared	0.6243	0.5972	0.6254	0.7217	0.7721	0.7466	0.7447	0.6632	0.6574	0.7713
P value (two-tailed)	0.0345	0.0416	0.0342	0.0155	0.0092	0.0121	0.0124	0.0257	0.0269	0.0093
P value summary	*	*	*	*	**	*	*	*	*	**
Number of XY pairs	7	7	7	7	7	7	7	7	7	7

To evaluate the relationship between circulating inflammatory profiles and disease severity, a Pearson correlation analysis was performed between inflammatory cytokines/signaling proteins (IL-23, IL-22, IL-19, IL-17, IL-6, JAK2, STAT3, IFN-γ, TNF-α, and MPO) and modified PASI. All inflammatory cytokines demonstrated a strong positive correlation with increased disease severity (Table 2).

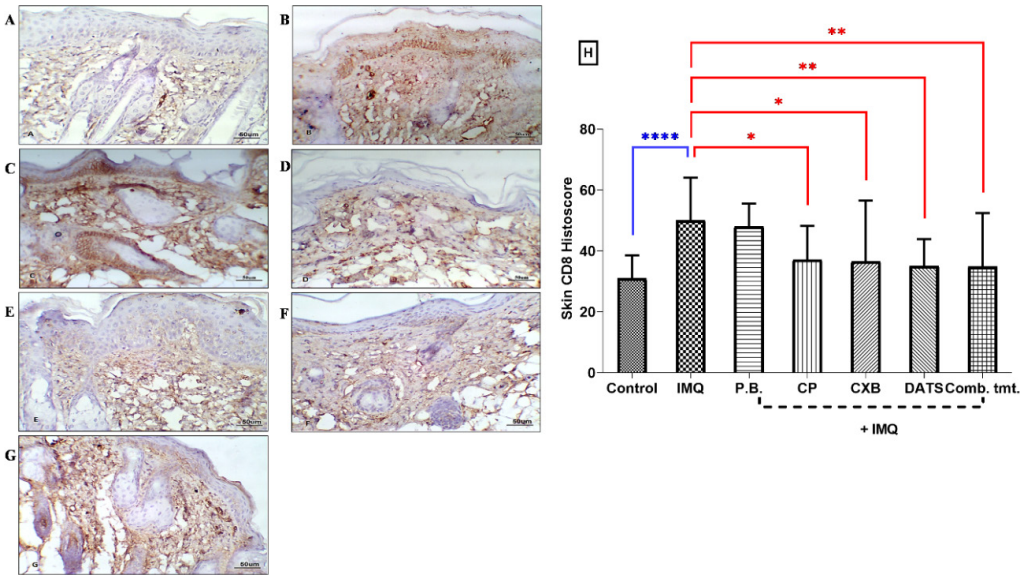

Figure 9. Effect of topical CXB and DATS emulgels, *per se* or in combination, on immunohistochemical analysis of skin CD8⁺ staining against IMQ-induced psoriasis in female BALB/c mice. Photomicrographs showed immunohistochemical staining of skin CD8⁺ from **A.** Control group; **B.** IMQ group; **C.** IMQ + P.B.; **D.** IMQ + CP; **E.** IMQ + CXB; **F.** IMQ + DATS; and **G.** IMQ + combined tmt. **H.** Skin CD8⁺ histoscore. Data were expressed as mean ± SD (n = 4/group), using one-way ANOVA followed by Tukey's multiple comparisons test. *$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$. ($R^2 = 0.2264$). CXB: celecoxib; DATS: diallyl trisulfide; IMQ: imiquimod; CD8⁺: cluster of differentiation 8; tmt.: treatment. Scale bar: 50 μm.

Table 3. Correlation between inflammatory cytokines, signaling proteins, and disease severity (number of scratch bouts/30 min).

	Scratch bouts/30 min vs. skin IL-23	Scratch bouts/30 min vs. skin IL-22	Scratch bouts/30 min vs. skin IL-19	Scratch bouts/30 min vs. serum IL-17	Scratch bouts/30 min vs. serum IL-6	Scratch bouts/30 min vs. ears JAK2	Scratch bouts/30 min vs. ears STAT3	Scratch bouts/30 min vs. serum IFN-γ	Scratch bouts/30 min vs. serum TNF-α	Scratch bouts/30 min vs. ears MPO
Pearson *r*	0.7671	0.8330	0.8230	0.8856	0.8586	0.8410	0.8578	0.8139	0.8485	0.8896
95% confidence interval	0.03330–0.9635	0.2145–0.9747	0.1838–0.9730	0.3978–0.9830	0.2985–0.9788	0.2399–0.9760	0.2959–0.9787	0.1571–0.9715	0.2644–0.9772	0.4138–0.9837
R squared	0.5885	0.6939	0.6773	0.7842	0.7371	0.7073	0.7358	0.6624	0.7200	0.7915
P value (two-tailed)	0.0441	0.0200	0.0230	0.0080	0.0134	0.0177	0.0135	0.0259	0.0158	0.0073
P value summary	*	*	*	**	*	*	*	*	*	**
Number of XY pairs	7	7	7	7	7	7	7	7	7	7

To evaluate the relationship between circulating inflammatory profiles and disease severity, a Pearson correlation analysis was performed between inflammatory cytokines/signaling proteins (IL-23, IL-22, IL-19, IL-17, IL-6, JAK2, STAT3, IFN-γ, TNF-α, and MPO) and the number of scratch bouts/30 min. All inflammatory cytokines and signaling proteins demonstrated a strong positive correlation with increased disease severity (Table 3).

Discussion

The results showed that topical treatment with CXB, DATS, or their combination against IMQ-induced psoriasis in BALB/c mice markedly mitigated psoriasis severity indices, as shown by reduced PASI scores and scratch bouts. CXB and DATS suppressed IL-23/IL-22/IL-19/IL-17 and IL-6 and reduced total protein levels of JAK2/STAT3, as well as TNF-α and IFN-γ levels and MPO content. Additionally, both treatments reduced 5-HT levels, suggesting a serotonergic correlation with their antipsoriatic action.

IMQ-exposed mice showed high PASI scores; the reduced PASI scores and scratch bouts following CXB and DATS treatment indicate effective suppression of IMQ-induced skin symptoms. P.B. significantly reduced these indices compared with the IMQ group; however, they did not return to control levels. This effect likely reflects the

emollient properties of emulgels, which can alleviate scaling and pruritus (Reich et al. 2020). Emollients remove excess stratum corneum, enhance hydration, reduce skin irritation, and soothe psoriatic skin. Still, their effectiveness as monotherapy is limited (Kowalska et al. 2025). This is reinforced by Heim et al. (2022), in which placebo treatment lowered epidermal thickness and improved targeted Psoriasis Area and Severity Index (tPASI) scores, yet did not significantly affect $CD8^+$ T cells in the epidermis or restore baseline conditions (Heim et al. 2022).

The findings showed that IMQ-exposed mice exhibited an increased number of scratch bouts, attributed to the pruritogenic effect of IMQ through direct interaction with TRPA1 and TRPV1 (Go et al. 2024). While these channels play a role in mediating itch sensation (Shirolkar and Mishra 2022), mounting evidence implies a more convoluted role in psoriasis. Notably, genetic deletion or pharmacological blockade of TRPA1, as well as sensory denervation of TRPV1, has been shown to exacerbate psoriatic dermatitis; consequently, modulating these receptors, rather than inhibiting them, may alleviate psoriasis (Kemény et al. 2018; Zhang et al. 2021; da Silva et al. 2026).

DATS, a garlic-derived polysulfide (Seki and Hosono 2025), is known for its anti-inflammatory properties (Nur Indriyani et al. 2026) via TRPA1 and TRPV1 activation (Sun and Dong 2016). Likewise, natural TRP channel agonists have revealed antipsoriatic action mediated by their anti-inflammatory effects. Mustard oil, which contains allyl isothiocyanate (a TRPA1 agonist) (Kemény et al. 2018), in addition to capsaicin (a TRPV1 agonist), has been proven to downregulate M1 macrophage polarization and lower the inflammatory mediators IL-1β, IL-6, IL-8, IL-18, TNF-α, and iNOS (Lv et al. 2021). These findings are supported by evidence that selective TRPV1 deletion increases TNF-α, IL-1β, and IL-6, leading to an augmented inflammatory response (Ueno et al. 2023). In addition to its TRPA1-mediated actions, H_2S provides antipsoriatic effects by activating transient receptor potential melastatin type 8, which supports epidermal barrier recovery (Denda and Nakanishi 2022). Additionally, H_2S counteracts ROS-activated NF-κB/COX-2 pathways, contributing to its antipruritic effects (Liang et al. 2024).

The antipruritic effects of CXB may be due to TRPV3 channel modulation (Martin et al. 2022), which is upregulated in psoriatic lesions and triggers the release of inflammatory mediators such as IL-1α, TNF-α, and IL-23 (Kim et al. 2024). Accordingly, selective antagonism of TRPV3 may be a beneficial strategy for itch treatment (Spyra et al. 2017). Supporting this, Stevens et al. (2019) demonstrated that a CXB nanoemulsion reduced pain and lowered TRPV3 expression in a pain model (Stevens et al. 2019).

Serotonin mediates bidirectional interactions between the skin and the neuroendocrine system, supporting its role in psoriasis pathogenesis (Martins et al. 2020). Younes and Bakry (2016) found that epidermal serotonin expression was notably higher in patients with psoriasis than in controls (Younes and Bakry 2016), and serotonin receptor expression was elevated in psoriatic lesional skin (Turk and Kirchhof 2026). This is further supported by Sun and Dong (2016), who highlighted the involvement of TRP channels in itching through coupling with serotonin receptors (Sun and Dong 2016). In progressive psoriasis, serotonin promotes the proliferation of activated B and T lymphocytes, which express serotonin and 5-hydroxytryptamine (5-HT) receptors (Abdouh et al. 2001; Huang et al. 2004a).

Furthermore, serotonin promotes $CD4^+$ T-cell secretion of IL-2, IL-6, and IL-8, thereby accelerating keratinocyte hyperproliferation (Huang et al. 2004a) and IL-2/IFN-γ production via the $5\text{-}HT_1A$ receptor (Arreola et al. 2015). Additionally, serotonin enhances IL-16 release from $CD8^+$ T cells, attracting $CD4^+$ T cells to sites of inflammation (Laberge et al. 1996). Moreover, activated T cells can also synthesize and release serotonin, influencing the maturation of DCs (Katoh et al. 2006; Arreola et al. 2015). Mouse models indicate that serotonin is necessary for neutrophil recruitment to sites of acute inflammation, alongside other chemotactic stimuli (Duerschmied et al. 2013).

In the present work, both treatments attenuated IMQ-induced psoriasiform changes, which may be due to suppression of the elevated serotonin levels noted in the model group. This effect may be attributed to the suppressive effects of COX-2 inhibitors on mast cell degranulation (Chen et al. 2024) and the similar action exhibited by H_2S donors, such as fast-releasing (e.g., Na_2S) and slow-releasing (e.g., GYY4137) donors, which provide protection against acute pruritus and inflammation mediated by histamine and mast cells (Rodrigues et al. 2017). CXB and DATS individually stabilize mast cells, discouraging serotonin release (Koroleva et al. 2020; Chen et al. 2024), while their combination led to a further reduction in serotonin levels.

Topical IMQ application significantly increased spleen weight, corroborating findings by (Jabeen et al. 2020). This rise correlated with enhanced splenic B- and T-cell populations (Puhm and Boilard 2022). The results indicate that IMQ induces splenic extramedullary hematopoiesis, demonstrating systemic inflammatory effects beyond the skin (Yokogawa et al. 2014), and linking localized IMQ exposure to systemic immune modulation, T-cell recruitment, and elevated PASI scores (Mack et al. 2012). In contrast, CXB and DATS emulgels, *per se* or in combination reduced spleen weight, consistent with earlier studies confirming that CXB suppresses splenic proliferation and downregulates inflammatory cytokines and spleen-derived immune cells in a liver cirrhosis rat model (Tang et al. 2021). Likewise, DATS has been reported to lower spleen weight in BALB/c mice with leukemia (Hung et al. 2015). The reduction in absolute spleen weight with CP is a recognized side effect of corticosteroid treatment (Shimo et al. 1982). In addition, CXB and DATS treatments significantly reduced Baker's pathology scores and histopathological abnormalities compared with the standard CP group, which showed severe skin thinning and atrophic hair follicles, a well-documented adverse effect of corticosteroids (Beebeejaun et al. 2023).

The IL-23/Th17 axis, particularly IL-17 production, appears to profoundly influence the emergence of psoriatic lesions (Potestio et al. 2024a). IL-23 is crucial for Th17 cell

activation and IL-17 secretion, which directly stimulates KCs, creating a self-perpetuating inflammatory loop that exacerbates inflammation and epidermal hyperplasia (Hawkes et al. 2017). In parallel, Th1 cells further sustain psoriasis through IFN-γ production (Johnson-Huang et al. 2012), while Th22 cells aggravate epidermal hyperproliferation via IL-22. In addition, keratinocyte-derived cytokines such as IL-19, IL-20, and IL-36 maintain this chronic inflammatory cycle (Saw and Song 2025).

IL-19, a downstream element of the IL-23/IL-17 axis and a marker of disease progression (Zhu et al. 2024), is produced by KCs in response to IL-17A, TNF-α, and IL-22. It enhances the effects of IL-17A by stimulating chemokine production that attracts neutrophils and Th17 cells, aggravating psoriatic inflammation (Witte et al. 2014; Li et al. 2025). Treatment with ixekizumab, an anti-IL-17A antibody, normalizes IL-19 levels and improves PASI scores (Konrad et al. 2019), which is consistent with the present results showing that CXB/DATS treatment caused a notable drop in IL-19 levels attributed to the decreased IL-17, TNF-α, and IL-22 levels recorded herein.

Myeloperoxidase (MPO) is produced by neutrophils and monocytes (Bos et al. 1978) and serves as a measure of neutrophil infiltration and as an immune cell marker in psoriasis (Abreu Velez et al. 2012), correlating with disease severity (Sangaraju et al. 2021). The MPO gene has been identified as a key disease-associated gene in psoriasis (Haskamp et al. 2020; Vergnano et al. 2020). MPO inhibition has been reported to reduce psoriasis severity in the IMQ mouse model (Neu et al. 2021), which corresponds with the results in the model group. Upon CXB and DATS treatment either alone or both together, MPO levels were reduced, which aligns with the decrease in skin MPO activity observed after topical CXB application following UVB exposure (Wulff et al. 2010). Likewise, DATS has been shown to mitigate naphthalene-induced oxidative liver damage by reducing serum TNF-α and IL-8, regulating inflammatory cell infiltration in lung tissues, decreasing MPO and NO production, and restoring GSH levels (Zhang et al. 2016).

Tumor necrosis factor α (TNF-α) promotes inflammation through COX-2 stimulation and PGE2 synthesis (Tran et al. 2026), which play roles in both initiating and resolving inflammation while supporting the shift from innate to adaptive immunity (Bozrova et al. 2013; Maseda et al. 2018). IL-6 contributes to the inflammatory cascade by forming the IL-6/IL-6R/glycoprotein 130 (gp130) complex, thereby activating the JAK2/STAT3 pathway that regulates cell proliferation, apoptosis, and inflammation (Kraakman et al. 2015; Rose-John et al. 2023). JAK/STAT activation promotes Th17 differentiation and IL-17 production, further exacerbating inflammation (Yang et al. 2025). Consistently, STAT1 and STAT3 expression levels are notably higher in psoriatic lesional areas (Andrés et al. 2013). This pathway has also been linked to cytokine-induced pruritus, suggesting that it could serve as a potential therapeutic target (Nakashima et al. 2019).

In the present study, CXB and DATS reduced levels of IL-6, JAK2, and STAT3 in the IMQ-induced model, which may be responsible for improved pruritus. This is in line with the reported antipruritic effects of the JAK inhibitor tofacitinib in patients with psoriasis (Bushmakin et al. 2015; Hashimoto et al. 2019; Komiya et al. 2020). This is consistent with findings that CXB treatment significantly downregulated phosphorylated STAT3 expression and other STAT3-related genes (Yang et al. 2014). Similarly, DATS mitigates skin toxicity in epidermal growth factor receptor inhibitor (EGFRI)-induced models by normalizing cytokine levels through inhibition of TLR4/NF-κB, JAK1/STAT3, and ERK pathways (Liu et al. 2019). Moreover, H_2S has been shown to protect against cardiac fibrosis by downregulating the JAK/STAT pathway and to mitigate colitis by inhibiting inflammatory signaling mediated by NFκB, STAT3, and proinflammatory proteins such as COX-2 (Lee et al. 2013). DATS has also shown effectiveness in suppressing STAT3 phosphorylation in both *in vitro* and *in vivo* models of prostate cancer (Chandra-Kuntal and Singh 2010).

The anti-inflammatory properties of CXB are largely attributed to its ability to inhibit COX-2 enzyme activity (Pomseethong et al. 2026), reducing PGE2 levels and inflammation (Ladjel-Mendil et al. 2025). Elevated PGE2 levels were detected in blister fluid from psoriatic skin (Reilly et al. 2000). PGE2 inhibits IL-22-binding protein, a regulator of IL-22 function (Voglis et al. 2018), an effect reversed by COX-2 inhibition. In addition, blocking PGE2-EP2/EP4 signaling also suppressed IL-23-induced Th17 cell activation and skin inflammation (Lee et al. 2019), with reduced IL-22 and IL-23 in treated groups.

Beyond its role in inflammation, PGE2 promotes pruritus through interaction with serotonin, since PGE2 enhances responses to serotonin (Fjellner and Hägermark 1979). Therefore, the antipruritic effect of NSAIDs stems from COX inhibition followed by suppression of PGE2 synthesis, which in part limits serotonergic reactions (Tong et al. 2022). In addition, PGE2 modulates T-cell effector functions, suggesting that COX-2 inhibitors can have anti-inflammatory effects independent of IL-23. This hypothesis, proposed by Napolitani et al. (2009) and supported by Garth et al. (2017), showed that CXB reduced IL-17A, IL-22, IL-1α, IL-1β, and IL-6 levels in mice after fungal exposure. Additionally, introducing a PGE2 agonist to lung cells from *A. fumigatus*-exposed mice increased IL-6, IL-17A, and IL-22 production (Napolitani et al. 2009; Garth et al. 2017).

Similarly, DATS has shown anti-inflammatory effects by reducing COX-2 expression and inflammatory cytokines, including TNF-α, IL-1β, and IL-6, in a valproate-induced hepatotoxicity model (Shaaban and El-Agamy 2017). It also inhibits inflammation by downregulating MyD88/NF-κB activity, thus decreasing NO and PGE2 production (Lee et al. 2018).

IMQ promotes the recruitment and expansion of $CD4^+$ and $CD8^+$ T cells (van der Fits et al. 2009; Orzan et al. 2025), which synchronize the elevated immune response through increased expression of inflammatory cytokines (Vu et al. 2021). Treatment with CXB or DATS suppressed $CD4^+$ and $CD8^+$ T-cell histoscores, as observed herein. Indeed, CXB treatment reduced $CD4^+$ and $CD8^+$ T-cell levels and IFN-γ-expressing $CD8^+$ T

cells in a chromium-induced allergic challenge model (Sitalaksmi et al. 2019). Likewise, diallyl sulfide (DAS) showed potential in treating benign prostatic hyperplasia by reducing immune-inflammatory responses, as indicated by lower $CD4^+$ T-cell protein expression and inflammatory cytokines such as IL-6 and IL-17 (Elbaz et al. 2020).

Although NSAIDs have been reported to exacerbate psoriasis (Dogra and Kamat 2019), a large cohort study from the Nurses' Health Study (NHS) found no significant association between regular NSAID use and an increased risk of developing psoriasis, and the current body of evidence does not warrant advising against the use of NSAIDs in patients with psoriasis (Balak and Hajdarbegovic 2024). Psoriasis plaques feature high levels of the COX-2 enzyme and inflammatory prostaglandins such as PGE2. By blocking this pathway directly in the skin, topical celecoxib reduces local tissue swelling and redness (Nitescu et al. 2022), while minimizing systemic exposure and avoiding the systemic imbalances associated with drug-induced psoriasis flares. Moreover, current clinical guidelines continue to recommend NSAIDs as a first-line treatment option for managing psoriatic arthritis (Balak and Hajdarbegovic 2024).

The significant positive correlation between inflammatory cytokines and the JAK/STAT pathway on the one hand and the PASI score and number of scratch bouts on the other hand is reinforced by both Li et al. (2026), who demonstrated that JAK/STAT signaling proteins correlate with psoriasis severity and Gupta et al. (2025), who reported that elevated serum levels of TNF-α, IL-6, and IL-17 also correlate with psoriasis severity, indicating that these cytokines may serve as reliable biomarkers for disease activity and personalized treatment strategies (Gupta et al. 2025).

While the findings are based on an animal model, they highlight a potential new therapeutic target for psoriasis. Specifically, the crucial inflammatory cytokines identified here could be modulated using topical CXB and DATS emulgel, offering a promising avenue for future clinical evaluation in patient cohorts with incipient psoriasis.

Limitations

A limitation of the present study is that only the total protein levels of JAK2 and STAT3 were evaluated, rather than their respective phosphorylated states (p-JAK2 and p-STAT3). Because phosphorylation is critical for the functional activation and nuclear translocation of these signaling molecules, the lack of phospho-specific data precludes definitive confirmation of active pathway status. However, the observed downregulation of total JAK2 and STAT3 abundance strongly suggests depletion of the pathway's core machinery. Future investigations utilizing phosphorylation-specific assays and downstream target genes are warranted to fully elucidate the precise inhibitory dynamics of this treatment on JAK/STAT signaling, as well as to confirm serotonin receptor expression and downstream components. Regarding dosing, only a single concentration was used per treatment as an initial screening phase to establish effectiveness; future studies are required to characterize the full dose-dependent profiles. Additionally, while the current study focused mainly on the primary therapeutic effect, no signs of visual or microscopic acute skin irritation were observed in the treated areas during the observation period. Skin irritation, epidermal toxicity, systemic toxicity, and organ histopathology assessments were not performed here, and these specific tests are planned for an immediate preclinical follow-up study. Evaluation of pharmaceutical attributes such as viscosity, spreadability, drug content uniformity, *in vitro* release, skin permeation, and enhanced skin penetration or retention is also required. Pharmacokinetic and skin deposition studies, along with long-term stability studies, would be valuable for future translational development toward a clinical topical dosage form. The lack of a solvent-matched vehicle control containing dimethylformamide (DMF) is a limitation, as baseline responses to DMF may influence the results. While the primary findings should be consistent, future studies should include a matched vehicle control to better distinguish the target compound's unique effects. In addition, the study design does not allow for definitive conclusions regarding equivalence or comparative safety relative to corticosteroid therapy.

Finally, while the data clearly demonstrate that CXB/DATS modulates key endpoint biomarkers within the IL-23/IL-17 axis, the functional kinetic responses of specific isolated immune cell subsets were not directly evaluated. Because the acute IMQ-induced model relies heavily on rapid innate immune activation and local keratinocyte proliferation, the endpoint biomarker and histopathological data provide strong evidence of direct therapeutic efficacy. However, future studies incorporating detailed functional immune assays will help elucidate the deeper cellular mechanisms and long-term adaptive immune effects of this intervention.

Conclusion

The main goal of the current study was to investigate the potential effects of topical emulgels of CXB, DATS, or their combination against psoriasis-like dermatitis induced by IMQ. The most obvious finding to emerge from this study is that CXB and DATS appear to alter the immune response through distinct yet interconnected cascades. These include IL-23/IL-22/IL-19/IL-17, IFN-γ/TNF-α/MPO, IL-6 and JAK2/STAT3 total proteins, as well as serotonin levels – mediators commonly implicated in the complex network of psoriasis-related inflammation. This modulation was also associated with relief of pruritus, the most distressing symptom of psoriasis. This study provides a glimpse into the potential antipsoriatic effects and prospects of CXB/DATS.

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Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

Experiments on animals: The study protocol was approved by the Ethics Committee of the Faculty of Pharmacy, Cairo University (permit number: PT 2656) and followed the US National Institutes of Health (NIH Publication No. 85-23, revised 2011) and ARRIVE guidelines. All efforts were made to minimize animal suffering during the study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Artificial Intelligence (AI) use

The authors accept full responsibility for the content of the manuscript, including the disclosure of any use of AI.

Regarding the use of AI in the preparation of this manuscript, the authors declare the following: Quillbot.

Used for: Language, style and writing.

QuillBot was used for summarizing and paraphrasing; after using this tool, the authors reviewed and edited the content as needed. The authors take full responsibility for the final text.

Funding

No funding was reported.

Author contributions

Maha M. Kamel: conceptualization, methodology, investigation, formal analysis, visualization, and writing an original draft; Hala F. Zaki: conceptualization, writing-reviewing and editing and supervision; Rofida A. Saleh: writing-reviewing and editing and supervision; Shirley R. Henry: histopathological examination, analysis and interpretation of data; Michael K. Ibrahim: conceptualization, writing-reviewing and editing and supervision; Mohamed Mofreh Bakr: methodology; Dalia M. N. Abouhussein: methodology, and formulation Mostafa A. Rabie: conceptualization, writing-reviewing and editing and supervision.

Data availability

The corresponding author can provide the data that were utilized to support this study's conclusions upon reasonable request.

Supplementary material 1

Supplementary information

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Data type: docx

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Link: https://doi.org/10.3897/pharmacia.73.e205623.suppl1