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Protective effect of cinnarizine on imiquimod-induced mouse model of psoriasis

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ABSTRACT: Psoriasis is defined as a series of events. It starts as dermatitis and eventually advances to more extensive inflammation and elevated oxidative stress. The objective of the study is to investigate the possible anti-psoriatic effect of topical cinnarizine on imiquimod-induced psoriasis in mice based on observational, histopathological, and biochemical outcomes. This study included 32 Swiss albino mice who divided into 4 groups (8 for each group) as the following: Group I (control group) was neither induced nor treated and the other three groups were induced for psoriasis by using imiquimod (IMQ) once a day for 6 days and two of these groups subjected to different interventions for eight consecutive days, including topical clobetasol and cinnarizine ointment. All studied groups subjected to Baker and Psoriasis Area Severity Index (PASI) scores assessment in addition to the measurement of interleukin (IL)-17, Tumor Necrosis Factor-alpha (TNF-α), malondialdehyde (MDA), and Ki-67 levels. The result of the study showed that topical cinnarizine significantly reduced the inflammatory signs of the psoriatic lesions, and these findings were supported by the histopathological examination. Additionally, topical cinnarizine significantly decreased IL-17, as well as TNF-α levels. They also reported an important drop in oxidative elements like MDA, and proliferative elements like Ki-67 when compared with the non-treated IMQ-induced psoriatic mice group. It was concluded that topical cinnarizine (3%) ointment demonstrated significant anti-psoriatic activity when compared with induced non-treated group with an effect comparable to that of standard treatment used (clobetasol).

KEYWORDS: Cinnarizine; Clobetasol propionate; Imiquimod-induced psoriasis; Inflammatory skin diseases; Psoriasis.

1. INTRODUCTION

Psoriasis is a chronic inflammatory dermatological disorder characterized by flaky, thicker, reddish skin plaques. Immune system and genetic components, as well as environmental influences (such viral infections and trauma), all appear to have an impact on psoriasis. The three main histologic features of psoriasis are inflammatory leukocyte infiltration, proliferation of dermal blood vessels, and epidermal hyperplasia. These features are primarily found in the dermis [1, 2]. In recent years, various other concurrent medical conditions have been postulated as being linked to psoriasis' recurrent inflammatory state. There is accumulating proof that psoriasis is connected with autoimmune conditions like rheumatoid arthritis, lupus erythematosus, Celiac disease, irritable bowel syndrome, and thyroiditis. Furthermore, patients with psoriasis are more likely to have metabolic syndromes, which include high blood pressure, high cholesterol, diabetes-related issues, and weight gain, in addition to psoriasis itself. These syndromes increase the risk of atherosclerosis and cardiovascular mortality [3, 4]. The maintenance stage of psoriasis is significantly influenced by the Tumor necrosis factor (TNF-α) / Interleukin (IL)-23/IL-17 axis. An important factor in the development of psoriasis is IL-17. Innate immunity can also create IL-17 independently of IL-23, despite the widespread belief that Th17 cells are produced by IL-23 [5]. In numerous types of cells, abnormalities in the synthesis and clearance of reactive oxygen species (ROS) result in cellular oxidative stress, which is linked to risk factors for the development of autoimmune illnesses [6-10]. Some illnesses distinguished by excessive angiogenesis, including psoriasis, are caused by disruptions in the mechanisms of normal physiological angiogenesis. The Ki-67 antigen, a combination of proteins generated at every phase of the cell cycle. As a result, it acts as a marker for cells which are actively dividing [11, 12].

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The two main methods for managing psoriasis are topical therapies (steroidal drugs and vitamin D3 analogs) and systemic therapies (retinoids like acitretin, PDE inhibitors like apremilast, antimetabolites like methotrexate, immunosuppressive drugs like cyclosporine, and phototherapies like PUVA) [13, 14]. Several anti-psoriatic biologics are available, such as anti-TNF-α (adalimumab, certolizumab, etanercept, and infliximab), anti-IL-17A (ixekizumab, secukinumab), and anti-IL-23 (guselkumab, risankizumab, and tildrakizumab) [15].

Cinnarizine is a piperazine analogue having the chemical name 1-(diphenyl methyl)-4-(3-phenyl-2-propenyl) and employed to treat motion sickness, nausea, vomiting, migraine, and vertigo/Meniere's illness. Additionally, it helps with vestibular problems from other origins [16]. Cinnarizine efficiently blocks histamine receptors, serotonin receptors, dopamine receptors, GABA receptors, and calcium channels, making it an appealing option for experimental research and exploration. There have been claims that cinnarizine possesses anti-inflammatory and anti-nociceptive abilities. This medication suppressed croton oil- or capsaicin-induced ear swelling in mice and prevented carrageen-induced edema in rats' hind paws [17]. Further, cinnarizine alleviates the rat model of ovalbumin-induced asthma by halting the production of pro-inflammatory cytokines, immunoglobulin E (IgE) formation, eosinophilic invasion, and oxidative and nitrosative distress [18]. Furthermore, cinnarizine was shown to suppress melanogenesis, rendering it an effective skin-whitening substance for treating hyperpigmentation [19]. Cinnarizine treatment also works to mitigate a model of CCL4-induced liver damage [20]. Besides, cinnarizine, administered intraperitoneally or intrathecally produced dose-related pain-relieving effect in rats [21]. The drug also inhibited acetic acid writhing test in mice in a dose-related way [22, 23]. Moreover, cinnarizine alleviated the formation of ulcerative lesions in a model of ethanol-induced gastric damage[24]. Similarly, cinnarizine exhibits anti-oxidative properties by combating the memory deterioration caused by haloperidol and restricting brain oxidative damage in mice [25].

This study aimed to evaluate the potential anti-psoriatic effects of topical cinnarizine treatment using a mouse model of imiquimod-induced psoriasis and compared its effectiveness with that of the standard drug clobetasol propionate.

2. RESULTS

It was demonstrated that the induced, non-treated group had significantly higher Baker's and cumulative Psoriasis Area Severity Index (PASI) scores compared to the healthy control group ($p<0.05$). However, clobetasol and cinnarizine treatment groups significantly decreased both the Baker's and cumulative PASI scores in comparison with the induced non-treated group ($p<0.05$). In addition, the cinnarizine group exhibited statistically considerable reductions in both Baker's and cumulative PASI scores versus the clobetasol group ($p<0.05$), Meanwhile, no significant changes were recorded between the clobetasol and cinnarizine groups ($p>0.05$) as seen in Figure 1.

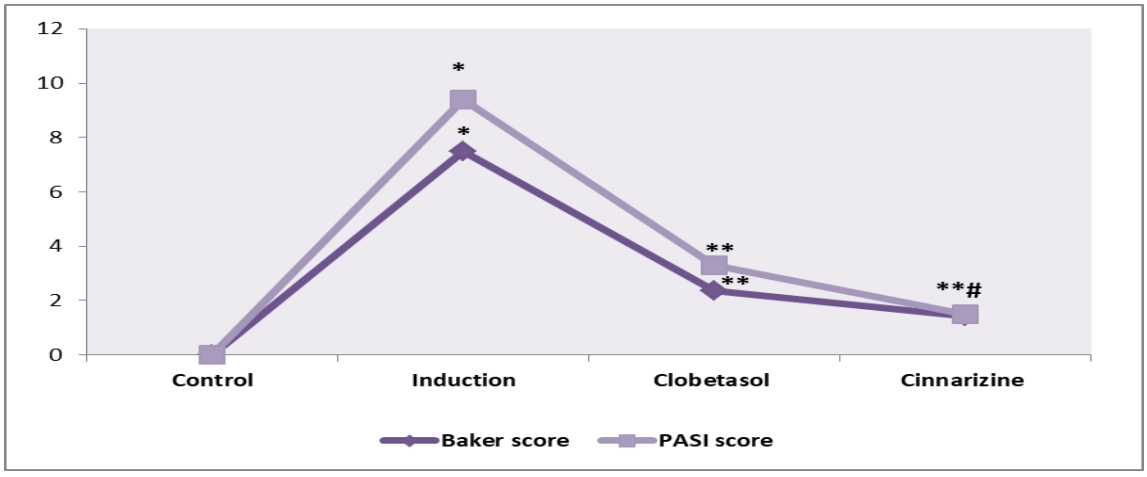

Figure 1. Effects of the studied drugs on the cumulative PASI and Baker's scores
* Significant at ($p<0.05$) versus the control group; ** Significant at ($p<0.05$) compared to the induction group; # Significant at ($p<0.05$) versus the clobetasol group.

In the present work, the results demonstrated that the induced, non-treated group showed significantly greater amounts of tissue inflammatory molecules TNF-α and IL-17 than the normal controls ($p<0.05$). The clobetasol and cinnarizine groups significantly diminished the amounts of tissue inflammatory molecules TNF-α and IL-17 compared with the induced, non-treated group ($p<0.05$). Meanwhile, no significant changes were recorded between the clobetasol and cinnarizine groups regarding TNF-α and IL-17 amounts ($p>0.05$) as seen in Figure 2.

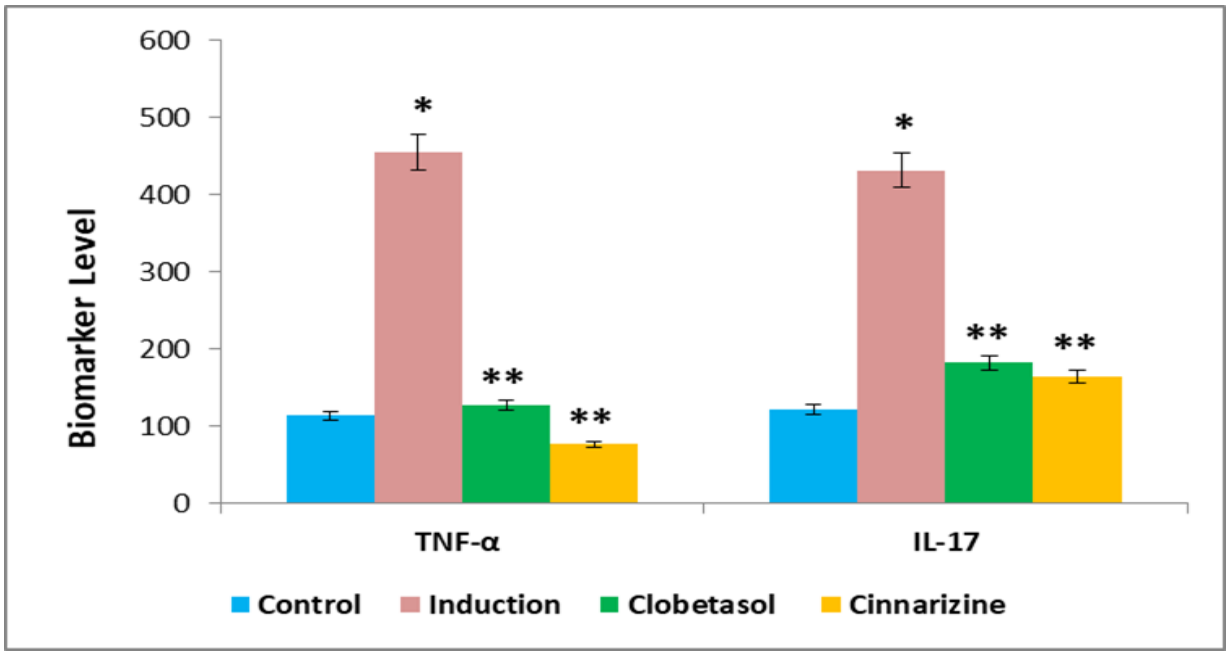

Figure 2. Effects of the studied drugs on the inflammatory parameters TNF-α and IL-17. TNF-α = Tumor necrosis factor alpha, IL= Interleukin.
* Significant at ($p<0.05$) versus the control group; ** Significant at ($p<0.05$) compared to the induction group; # Significant at ($p<0.05$) versus the clobetasol group; MDA= malondialdehyde.

The induced, non-treated group reported significant elevations in tissue concentrations of the oxidative MDA and proliferative KI-67 indicators when compared to the control group ($p<0.05$). Clobetasol and cinnarizine significantly decreased the levels of the oxidant MDA and proliferative KI-67 indicators in comparison with the induced, non-treated group ($p<0.05$). Likewise, the cinnarizine group experienced a significant diminution in MDA levels relative to the clobetasol group, while there were no significant variations between the clobetasol and cinnarizine groups in terms of KI-67 as seen in Figure 3.

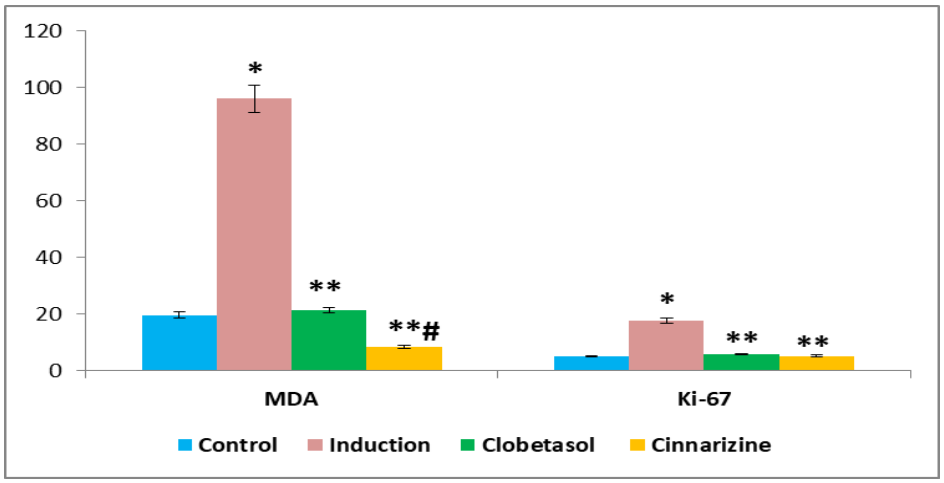

Figure 3. Effects of the studied drugs on the oxidative MDA and proliferative KI-67 indicators.
* Significant at ($p<0.05$) versus the control group; ** Significant at ($p<0.05$) compared to the induction group; # Significant at ($p<0.05$) versus the clobetasol group; MDA= malondialdehyde.

In the current study, the histopathological sections for the untreated control group showed normal dermal and epidermal layers. There was no hyperkeratosis, parakeratosis, or acanthosis in the keratin layer, and no lymphocyte infiltrating in the dermal layer as seen in Figure 4A (H&E 10X). The induced non-treated group by imiquimod showed significant changes including the development of Munro abscesses, hyperkeratosis, abnormally thick epidermis, thinning over papillae, the existence of rete ridges, and a lack of granular as seen in Figure 4B (H&E 10X).

The histological characteristics of the clobetasol (0.05%) group included a modest infiltrate of inflammatory cells and decreasing in the epidermal thickness. When compared to the induction group, clobetasol exhibited a substantial preventive and restorative impact on psoriatic lesions as seen in Figure 4C (H&E 10X). Cinnarizine ointment 3% treatment showed a highly significant attenuation ($p<0.05$) in the histopathological changes as compared to the induction group. This attenuation included the absence of Munro abscesses, acanthosis, and hyperkeratosis. Additionally, there was less degree of thickening within the epidermis and mild lymphocyte infiltration as seen in Figure 4D (H&E 10X).

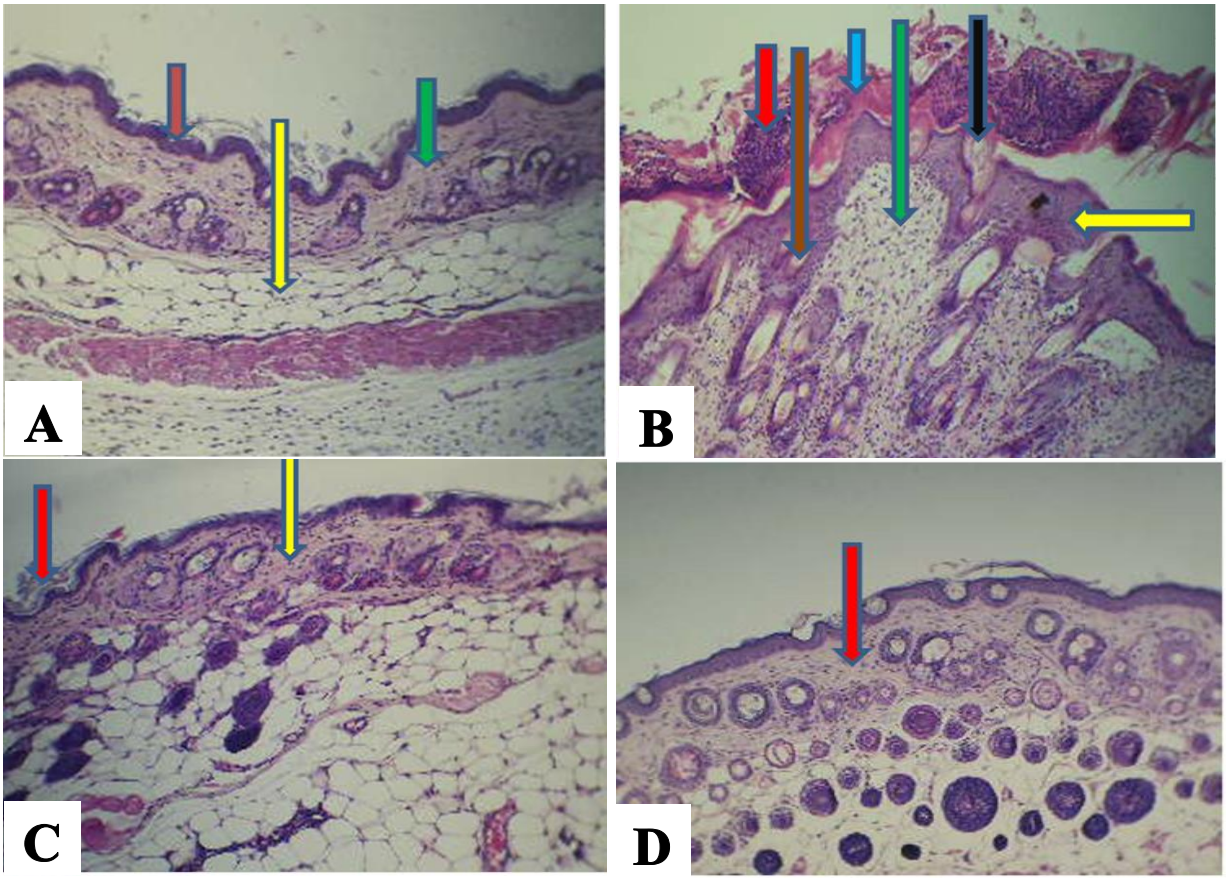

Figure 4. Effects of the studied drugs on histopathological changes A. The skin section from the control group shows the three skin layers (red arrow epidermis layer, green arrow dermis layer, yellow arrow SC layer); H&E, 10X. B. Skin section from the induction group shows Munro abscess (red arrow), hyperkeratosis (blue arrow), parakeratosis (black arrow) presence of rete ridges (brown arrow), lymphocyte infiltration (green arrow), and acanthosis (yellow arrow); H&E, 10X. C. Skin section from the clobetasol group shows hyperkeratosis (red arrow) and mild lymphocyte (yellow arrow); H&E, 10X D. Skin section from the cinnarizine (3%) group shows mild lymphocyte (red arrow); H&E 10X.

3. DISCUSSION

Psoriasis, as described earlier, is regarded as an immune-driven, persistent inflammatory condition [26, 27]. It is caused by an increase in keratinocyte turnover and the interaction of immune cells in the dermis, leading to epidermal hyperplasia, and is characterized by the appearance of erythematous plaques covered with silvery adhering scales [28, 29]. Several prior studies have shown that imiquimod, applied once daily to the dorsal skin of mice for 6–8 days can cause skin lesions that resemble psoriasis, including erythema, desquamation, and acanthosis. It also considerably increases proliferative, oxidative, and inflammatory parameters [30-32]. Further research elucidates imiquimod's role in psoriasis induction, since

it amplifies TNF-α, IL-17, and IL-23 levels and closely mimics the histological and phenotypic characteristics of human psoriatic lesions [30, 33].

However, clobetasol, the standard medication used in this trial, markedly alleviated the symptoms of imiquimod-aggravated psoriasis, Clobetasol's wide range of activities, which include anti-inflammatory characteristics, decreased neutrophil and monocyte recruitment, decreased lymphocyte reactivity, vasoconstrictive properties, antiproliferative/antimitotic effects, and decreased mast cell density and reactivity, including immunoglobulin E sensitization, are the reason for the drug's effect against psoriasis [32, 34, 35].

In the present study, the topical of 3% cinnarizine ointment effectively mitigated the upregulated levels of inflammatory biomarkers (IL-17, and TNF-α), oxidative biomarkers (MDA), proliferative biomarker (Ki-67 protein), histopathological Baker's scores, and observational PASI scores. While no prior research has evaluated the efficacy of topical cinnarizine in treating psoriasis, some studies have examined its impact on other similar immune-mediated diseases, involving an experimentally provoked model of ulcerative colitis, where cinnarizine drastically lowered the levels of oxidative markers like MDA and myeloperoxidase (MPO), inflammatory markers like TNF-α and IL-4, and adhesion molecules like endothelial (E)-Selectin and intercellular adhesion molecule-1 (ICAM-1) in the colonic tissues [36]. However, these anti-inflammatory benefits of cinnarizine might originate from its capacity to hamper histamine (H1) receptors, which is thought to be an effector in the emergence of dermatological conditions such as urticaria, Darier disease, alopecia, acne, and psoriasis [37]. Apart from that, our results were consistent with previously published investigations that demonstrated cinnarizine acts as an antioxidant by restoring the activity of glutathione (GSH) and superoxide dismutase (SOD), which helps dampen the oxidative impact [38]. At the same time, our findings align with a former analysis suggesting that using cinnarizine greatly diminished inflammation-related scores in a bronchial asthma murine prototype by lowering levels of TNF-α, IL-5, IgE, GSH, SOD, and nitric oxide end products (NOx) back to normal [18]. Likewise, cinnarizine could potentially alleviate microwave-elicited cerebral inflammation through diminishing IL-1β cytokine levels and Ca2+ excess. Additionally, Abdel-Salam et al. (2007) proved that cinnarizine has anti-inflammatory and antioxidant impacts in an animal model of acetic acid-challenged visceral inflammation, owing in part to its antihistamine or catecholamine reuptake-blocking characteristics [39]. Similarly, cinnarizine therapy reduced haloperidol-exacerbated neurotoxicity in mice by substantially limiting MDA production and substantially boosting GSH content [25].

4. CONCLUSION

Topical cinnarizine (3%) ointment demonstrated significant anti-psoriatic activity when compared with induced non-treated group with an effect comparable to that of standard treatment used (clobetasol). Anti-psoriatic effect is probably due to it anti-inflammatory, anti-oxidant and anti-proliferative properties which appeared in its influence on the levels of TNF-a, IL-17, MDA and KI-67.

5. MATERIALS AND METHODS

5.1. Materials

5.1.1. Experimental animals:

Thirty-two healthy albino mice weighing 24–30 g and aged 11–15 weeks were obtained from the Iraqi Center for Cancer Research and Medical Genetics and housed in a well-ventilated non-pathogenic environment with adequate water and food supply throughout the study. The animals had a one-week acclimatization period prior to the start of the experiment in a controlled environment at 25 °C. The study was conducted between October 2023 and February 2024. The study was carefully reviewed for ethical and scientific care and received approval from the Institutional Review Board (IRB) of the College of Medicine at AL-Nahrain University on October 25, 2023, as per Document IRB/136 and approval number UNCOMIRB20240631.

5.1.2. Drugs and reagents

Clobetasol propionate ointment was obtained from the State Company for Drugs Industry and medical Appliances Samarra/ Iraq (SDI). Imiquimod was provided by Meda Pharmaceuticals, Solna, Sweden, under the brand name Aldara® 5% Cream whereas cinnarizine is obtained as a powder from Hangzhou Hyper Chemicals Limited Company (China).

5.2. Methods

5.2.1. Pharmaceutical preparation of 3% cinnarizine ointment:

The levigation method was used to prepare the ointment in which 0.45 gram of cinnarizine were dissolved in 2 milliliters of levigation solution (castor oil), then added to 14.55 grams of ointment base (paraffin), and well mixed to produce a smooth, grit-free mixture [40] .

5.2.2. Experimental design

32 mice subjected to dorsal shaving with an electric razor to expose a 2 cm area of back skin. The duration of the experiment is 14 days and the mice subjected to the current study were divided randomly into 4 groups, each consisting of 8 mice, that received as follows:

- **Group I (apparently healthy) group:** consisted of normal, healthy mice that had not received any type`3 of treatment.
- **Group II (Induction) group:** Mice were administered topical imiquimod cream (5%) at a dosage of 62.5 mg for up to 6 days [41].
- **Group III Clobetasol-treated group:** Mice were given imiquimod (as in Group II), followed by topical clobetasol ointment (0.05%) at a dose of 0.25 g/kg twice a day for an extra 8 days [30, 32].
- **Group IV Cinnarizine-treated group:** Mice were given imiquimod (as in Group II), followed by topical cinnarizine ointment applied twice a day with a two-hour interval between. This cycle of treatment continued for 8 days.

5.2.3. The psoriasis area and severity index (PASI)

Measures of skin erythema, scaling, and thickness were used to determine the degree of skin inflammation and lesion severity to determine the severity of skin psoriasis. PASI for all studied groups was evaluated on a scale from 0 to 4. "0" denotes none, "1" denotes slight, "2" denotes moderate, "3" denotes marked, and "4" denotes severe. The cumulative PASI scores were computed by adding the additive values for erythema, scaling, and thickness to determine the severity of the lesion [41, 42].

5.2.4. Preparation and sampling of animals

On day 14, ketamine (80 mg/kg) and xylazine (10 mg/kg) were administered intraperitoneally (IP) to all animals. After undergoing full anesthesia, all mice were killed by exsanguination [43]. Dorsal shaved skin samples (4 mm) were collected, and placed in a 10% neutral buffered formalin solution for histological examination [44].

5.2.5. Preparation of tissue homogenate

One gram of newly extracted back skin has been kept in a 9-ml phosphate-saturated buffer solution with a pH of 7.2. Using a pestle and mortar, the tissues were homogenized before being centrifuged for 10 minutes at 5000 rpm at a low temperature. Supernatants were kept for additional analysis at -80 °[45].

5.2.6. Histopathological examination

A sample of skin tissue from each mouse, measured to be about one-centimeter square, had to be prepared for the histological investigation. It was subsequently fixed with 10% formalin and processed. The sample was dehydrated by immersing it in various percentages of ethanol (70, 80, 90, 95, and 100%) for two hours each. After dipping the specimen in liquid paraffin at about 55-60 °C, xylol was added. [46, 47] Tissue was embedded in paraffin on a cold plate, and then a paraffin block was made. A section thickness of 5 mm was obtained with a microtome and stained with eosin and haematoxylin [48]. After that, the samples were examined under a microscope and scored using Barker's scoring system, which gives a number between 0 and 10 to indicate whether any pathological changes are present [49].

5.2.7. Measurement of inflammatory, oxidative, and proliferative biomarkers

The quantities of TNF-α, IL-17, malondialdehyde (MDA), and KI67 in mouse skin tissues were measured using sandwich enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions (Cloud-Clone Corp) [50-52].

5.3. Statistical analysis

Data stored and analyzed by using Microsoft Excel 365 and SPSS version 26. Among studied groups independent t-test and one-way ANOVA were used for continuous variables to assess the differences between these groups. Levels of numerical parameters were expressed as Mean± standard deviation (SD) and P- values were considered significant at a level (P<0.05) or highly significant at (P<0.001) [53, 54].

Author contributions: Concept – A.A.; Design – B.A., A.A.; Supervision – A.A.; Resources – B.A.; Materials – B.A.; Data Collection and/or Processing – B.A.; Analysis and/or Interpretation – B.A., A.A.; Literature Search – B.A., H.S.; Writing – B.A., H.S.; Critical Reviews – A.A., H.S.

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