



Original Article

## Evaluation of anti-psoriatic activity of selected phytochemicals on UV-induced psoriasis in mouse tail model

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### ABSTRACT

**Objectives:** To evaluate anti-psoriatic activity of Phytochemicals on UV-Induced psoriasis in mouse tail model.

**Materials and Methods:** Anti-psoriatic activity of selected phytochemicals on UV-Induced psoriasis in mouse tail model. The animals were dividing into 05 groups and each group contain 5 animals. Disease control group did not receive any treatment only exposure to UV-light, vehicle control treated with simple ointment, standard group treated with salicylic acid (1%w/w) ointment, remaining group are treated 1% and 2% selective phytochemical at two concentrations of ointment to topically on the tail skin. And the data were analysed using *one way ANOVA* followed by *two-way ANOVA* (Dunnett's multiple comparisons test).

**Results:** There was significant decrease in epidermal thickness ( $P < 0.05$ ) as compared with control group. In 2% phytoconstituents has shown a significant reduction in the total epidermal thickness  $8.4^{****} \pm 0.748$ ,  $7.6^{**} \pm 0.6781$  and  $8^{*} \pm 0.8366$  in geraniol, glycyrrhizic acid and ellagic acid treated group, when compare to the disease induced animal, there was no lesion of Munro's microabscess, capillary loop dilation along with elongation of rete ridges in the section of skin of rats. Psoriasis Severity Index was reduced in test treated groups as compared with that of disease control group. It was slowly reduced to 2<sup>nd</sup> week, totally (55-70%) reduction in PSI is observed at the time of third week of treatment period.

**Conclusion:** The result of the study showed that the 2% of geraniol, ellagic acid, glycyrrhizic acid and hesperidin, exhibited significant activity on UV-induced psoriasis in rodents. The study implies that selected phytoconstituents are a promising research for further investigations to prove its anti-psoriatic activity.

**Keywords:** Psoriasis, UV-Ray, Hesperidin, Ellagic acid and geraniol

### INTRODUCTION

Psoriasis is a common inflammatory condition of human skin characterised by focal to coalescing raised cutaneous plaques with consistent scaling and variable erythema. Typical histologic features of psoriasis include epidermal hyperplasia (acanthosis) with elongated rete ridges, a less discrete epidermal granular layer (hypogranulosis), parakeratosis and leucocytic infiltration of the dermis and epidermis.<sup>[1]</sup> It is a chronic inflammatory disease of the skin characterised by epidermal hyperplasia, dermal angiogenesis, infiltration of activated T cells and increased cytokine levels.<sup>[2]</sup> An increase in mitotic activity in the stratum basale, abnormal keratinisation and elongation of

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the dermal papillae toward the skin surface result in a thicker-than-normal stratum corneum that desquamates to produce large, silvery scales (Griffiths and Voorhees, 1996; Barker, 1991; Krueger and Callis, 2003)<sup>[3]</sup> Cyclooxygenase (COX)-2 inhibiting nonsteroidal anti-inflammatory drugs, corticosteroids and immunosuppressants such as FK-506 and cyclosporine A for Th1 cells have been used clinically for psoriasis. Repeated application of corticosteroids on the dorsal skin of rats causes dramatic skin atrophy. FK-506 and cyclosporine A exhibit side effects, such as severe nephrotoxicity and neurotoxicity (Schafer *et al.*, 1996; Sakuma *et al.*, 2001; Friedman *et al.*, 2002). Clinically drugs like NSAIDs are inhibiting the COX-2 enzyme and suppress the inflammation along with suppression of immunity by corticosteroids routinely used for treatment of psoriasis.<sup>[4]</sup> Conventional therapies such as corticosteroids, Vitamin D3 analogues and calcineurin inhibitors are currently used as topical therapies in mild psoriasis.

Severe psoriasis often necessitates treatment with phototherapy or systemic agents including methotrexate, cyclosporine and acitretin.<sup>[5]</sup> Biologic therapies that act on the upregulated cytokine pathways have also been developed and approved for psoriasis treatment.<sup>[6]</sup> However, most of these regimens have well-documented arrays of adverse effects that seem to be the main factor hampering patients' adherence to long term. Repeated application of corticosteroids on the dorsal skin of rats causes dramatic skin atrophy. Psoriatic pathological features also include excessive proliferation and impaired differentiation of epidermal keratinocytes, likely mediated by a dysregulated immune system.<sup>[7]</sup> Some people may develop skin diseases that affect the skin, including cancer, herpes and cellulites. Some wild plants and their parts are frequently used to treat these diseases.

The use of plants is as old as the humankind. Natural treatment is cheap and claimed to be safe. Flavonoids, tannins, glycosides, monoterpenes and alkaloids have been considered as effective for the treatment of various disorders in humans.<sup>[8]</sup> All five selected compounds have been widely used as active ingredients in many pharmaceutical products due to their analgesic, anti-inflammatory, anti-pain and wound healing properties.<sup>[9-12]</sup> It has been demonstrated to control multiple signalling molecules and pathways that are involved in various biological processes, such as the cell cycle, cell survival and proliferation, apoptosis, autophagy and metabolism.<sup>[13-16]</sup> Multitarget therapeutic agents are more efficacious for the treatment of complex diseases, based on these parameters, we want to evaluate test compounds for the treatment of chronic skin disorders.

## MATERIALS AND METHODS

### Ethical approval

All the experiments were carried out on albino mice in Chalpathi Institute of Pharmaceutical Sciences. The

mice were divided into 12 groups and each group ( $n = 5$ ) animals were kept in separate cages for acclimatisation at a temperature  $25 \pm 2^\circ\text{C}$  and relative humidity of 52–55% with 12 h light/dark cycle 1 week before and before commencement of the experiment. They were kept on standard pellet diet *ad libitum* and drinking water throughout the study period. The protocol of experimental study was approved by the Institutional Animal Ethics Committee (IAEC) with IAEC approval (No: 12/IAEC/CLPT/2018-19; Dt: 05/01/2019).

### Test compounds

Hesperidin, Glycyrrhizic acid, ellagic acid and geraniol were purchased from Sigma-Aldrich.

### Qualitative analysis of phytochemicals

- a. Flavonoids (Hesperidin):
  1. Small quantity of hesperidin was dissolved in aqueous sodium hydroxide solution. Appearance of yellow colour indicates the presence of flavonoids.
  2. Shinoda test: Small quantity of sample was dissolved in alcohol. To this few pieces of magnesium followed by concentrated hydrochloric acid was added dropwise and heated. Appearance of magenta colour indicates the presence of flavonoids.
- b. Tannins (Ellagic acid):
  1. Ferric chloride test: Small quantity of ellagic acid was taken in test tube and it was boiled with distilled water and then filtered. To the filtrate, few drops of 5% ferric chloride solution were added. Violet colour is observed, it indicated the presence of tannins.
  2. Ellagic acid is taken into test tube to this 1% solution of gelatine containing 10% sodium chloride. White colour precipitated indicates the presence of tannins.
- c. Glycosides (Glycyrrhizic acid):
 

Foam test (saponin glycosides): A 10 mg of Glycyrrhizic acid powder was taken in 50 ml measuring cylinder, added water up to 25 ml of the measuring cylinder and marked it as point 'A.' Shake vigorously for 5 min. Allowed it to stand for 30 min. Now marked the final volume as point 'B' and measured the distance from 'A to B.' It shows the formation of foam with increasing volume. This indicates presence of 'Saponin glycoside.'
- d. Aromatic oils (Geraniol):
 

Terpenoid test (Salkowski test): A 5 ml of Geraniol was mixed with 2 ml of chloroform and 3 ml concentrated H<sub>2</sub>SO<sub>4</sub> was carefully added to form a layer. A reddish-brown colouration of the interface was observed; it showed positive results for the presence of terpenoids.

### Experimental animals and research design

- Mice of both sexes were taken and all groups of animals.
- Those groups treated as Group-1 (control animal), Group-2 (standard drug treated animals), Group-3 (1% hesperidin), Group-4 (2% hesperidin), Group-5 (1% ellagic acid), Group-6 (2% ellagic acid), Group-7 (1% Glycyrrhizic acid), Group-8 (2% Glycyrrhizic acid), Group-9 (1% geraniol) and Group-10 (2% geraniol).
- Salicylic acid ointment was applied to mouse tail of standard group.
- Remaining group animals were treated with respective test compound. This process is continued for 7 days.
- Later mice's were sacrificed; tails were collected and sent to histopathological studies.

### Induction of psoriasis

All groups of animals were exposed to UV light for 14 days to inducing psoriasis on tail part.

### Treatment application

After the development of psoriatic lesions on tail part of mice, regularly test compounds are applied on to the skin of animal tail for daily once with the help of cotton buds.

### Evaluation of anti-psoriatic activity of test compounds

Epidermal thickness of mice tail was determined to observe the severity of psoriasis, physical observation of animal skin including erythema, itching and silvery patches on tail region. Psoriasis score index was calculated for each group to compare the efficacy of test compounds with that of standard. Psoriasis area and severity index (PASI) scores were determined by evaluating the degree of erythema, thickening and scaling on the affected dorsal skin surface and ear pinna. PASI for each was measured on a 4-point scale (0 = none; 1 = slight; 2 = moderate; 3 = marked and 4 = very marked). The severity of skin inflammation was measured by the combined scores (erythema plus scaling plus thickening) giving a range of scores of 0–12. Histological parameters are also observed by collecting the tail skin of mice.

### Data analysis

The data generated were presented in frequencies, percentages and 'Mean  $\pm$  standard error mean' and analysed with Chi-square, one-way analysis of variance (ANOVA).

## RESULTS

### Acute dermal toxicity

Healthy young adult animals of commonly used laboratory strains were employed. Each animal was 8–12 weeks old which was selected and all animals' weights were within the range. The animals are acclimatised to the laboratory conditions for 5 days before the start of the study. Animals are randomly selected to use in the study and marked to provide individual identification. Approximately 24 h before the study, fur was being removed from the dorsal area of the trunk of the test animals by shaving. The test substance was applied uniformly over an area which is approximately 10% of the total body surface area. Test substances were held in contact with the skin with a help of porous gauze dressing and non-irritating tape throughout a 24 h exposure period. Animals were observed for signs of toxicity from 30 min to periodically during the first 24 h, with special attention given during the first 4 h. All animals were free from signs of toxicity.

### Anti-psoriatic activity

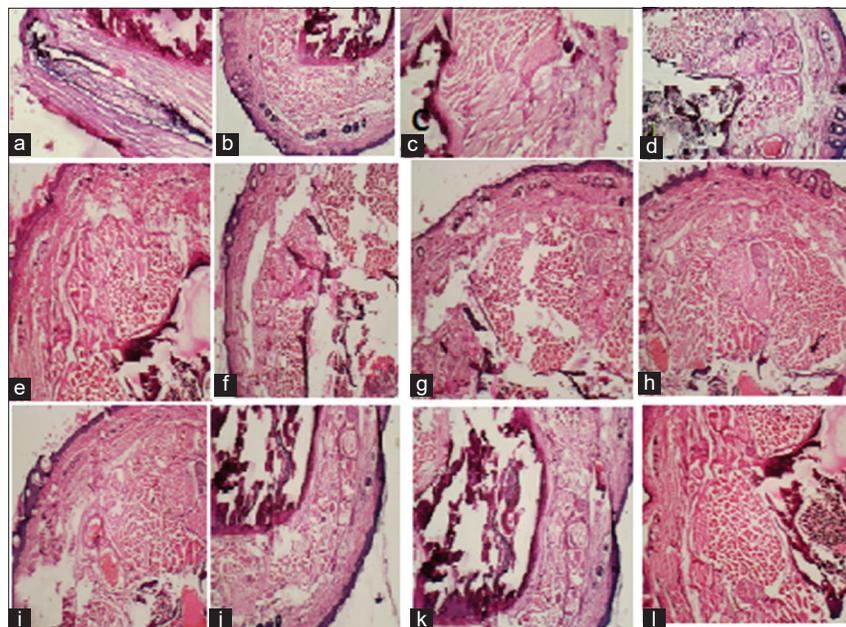
#### UV-induced model for psoriasis

The mean thicknesses of the epidermis, in control- and drug-treated animals, were tabulated [Table 1]. There was significant decrease in epidermal thickness ( $P < 0.05$ ) [Figures 1 and 2] as compared with disease control group. The section of disease control group showed regular elongation of rete ridges, capillary loop dilation with minimal grade lesion of diagnostic Munro's microabscess and marked increase in relative epidermal thickness as compared with other groups. In 1% of (geraniol, Glycyrrhizic acid and ellagic acid) treated group, there was a minimal grade lesion of elongation of rete ridges along with capillary loop dilation in the section and absence of Munro's microabscess. In 2% (Geraniol,

**Table 1:** Effect of phytochemicals on epidermal thickness of mouse tail in UV-induced psoriatic animals.

Treatment group	Hesperidin	Ellagic acid	Glycyrrhizic acid	Geraniol
Vehicle control (mm)	7.2 $\pm$ 1.3038	6.8 $\pm$ 0.7999	6.8 $\pm$ 0.3741	7.2 $\pm$ 0.583
Disease control (mm)	10.4 $\pm$ 1.1401	11.2 $\pm$ 0.4898	11.8 $\pm$ 0.7348	10.4 $\pm$ 0.678
Standard (mm)	7.4** $\pm$ 1.1401	6.8** $\pm$ 0.3741	5.8* $\pm$ 0.3741	7.4** $\pm$ 0.509
Test 1% (mm)	9.8 $\pm$ 2.3874	8.6 $\pm$ 1.4352	10.8 $\pm$ 1.7719	9.6 *** $\pm$ 0.927
Test 2% (mm)	10.4 $\pm$ 1.8165	8* $\pm$ 0.8366	7.6** $\pm$ 0.6781	8.4**** $\pm$ 0.748

The values are expressed in Mean $\pm$ SEM, \*\*\*mean  $P < 0.001$ , \*\* $P < 0.05$  results are significant compare to the disease control group. Analysis done by two-way ANOVA (Dunnett's multiple comparisons test)



**Figure 1:** Effect of phytochemicals on the pathological findings in the UV induced Psoriasis in mouse tail model. (a) Disease control, (b) Standard treated, (c) Vehicle control, (d) Disease control, (e) 1% Hesperidin, (f) 2% Hesperidin, (g) 1% Ellagic acid, (h) 2% Ellagic acid, (i) 1% Glycyrrhizic acid, (j) 2% Glycyrrhizic acid, (k) 1% Geraniol, (l) 2% Geraniol.

Glycyrrhizic acid, ellagic acid and hesperidin) treated group, there was no lesion of Munro's microabscess, capillary loop dilation along with elongation of rete ridges in the section of skin of rats [Figure 1]. In the standard group, there was absence of Munro's microabscess, capillary loop dilation along with elongation of rete ridges in the section showing significant therapeutic effects when compared with test-treated groups.

Psoriasis Severity Index was given to all individual group animals based on their signs and presence of erythema, itching and silvery scales on the skin. Disease control group gained a score of 2.0 at the 1<sup>st</sup> week, which increased to 2.8 at the end of the experiment (3<sup>rd</sup> week), while the standard group gained 2.1 at the 1<sup>st</sup> week, which was reduced to 1.0 at the 3<sup>rd</sup> week. Test-treated groups all initially gained scores of 2.4 to 2.8 at the 1<sup>st</sup> week, which were slowly reduced to the 2<sup>nd</sup> week, with a total reduction of 55–70% [Figure 3]. Reduction in PSI is observed at the time of the 3<sup>rd</sup> week of the treatment period. It reveals that bioflavonoids, tannins and lipid-derived terpenoids are more effective for the treatment of chronic disorders of human skin without complications.

## DISCUSSION

Skin is the largest exposed organ of the body and an easy target for allergic and immunologic reactions. Skin ailments, namely dermatitis, urticaria, angio-oedema and psoriasis,

**Table 2:** Effect of test compounds on Psoriasis Severity Index.

Group	1 <sup>st</sup> week	2 <sup>nd</sup> week	3 <sup>rd</sup> week
Disease control	2.0	2.5	2.8
Standard	2.1	1.5***	1.0***
Hesperidin 1%	2.0	1.7***	1.2***
Hesperidin 2%	2.3	1.6***	1.1***
Ellagic acid 1%	2.4	1.6***	1.2***
Ellagic acid 2%	2.3	1.3***	0.8***
Glycyrrhizic acid 1%	2.2	1.9***	1.3***
Glycyrrhizic acid 2%	2.4	1.7***	0.9***
Geraniol 1%	2.6	1.9***	1.1***
Geraniol 2%	2.8	1.7***	0.8***

Note: The results were obtained from one-way ANOVA, \*\*\* mean  $P < 0.0001$

are immune-mediated chronic and inflammatory disorders.<sup>[11]</sup> Psoriasis severely affects patients with the quality of life and the treatment being expensive.<sup>[12]</sup> Medicinal plants are considered safe, as for human health and are widely employed by traditional healers for the treatment of various diseases including psoriasis. Medicinal plants are known to be a rich citadel of a variety of chemical compounds and have attracted researchers' attention to find new treatments for psoriasis.<sup>[17]</sup> Screening of anti-psoriatic activity of various phytoconstituents was carried out using UV-induced psoriasis in mouse tail. The irradiated mice skin treated with selected phytoconstituents at 2% has shown a significant reduction in the total epidermal thickness  $8.4^{***} \pm 0.748$ ,  $7.6^{**} \pm 0.6781$  and  $8^{*} \pm 0.8366$  in geraniol, Figure 2 Glycyrrhizic acid and ellagic acid treated

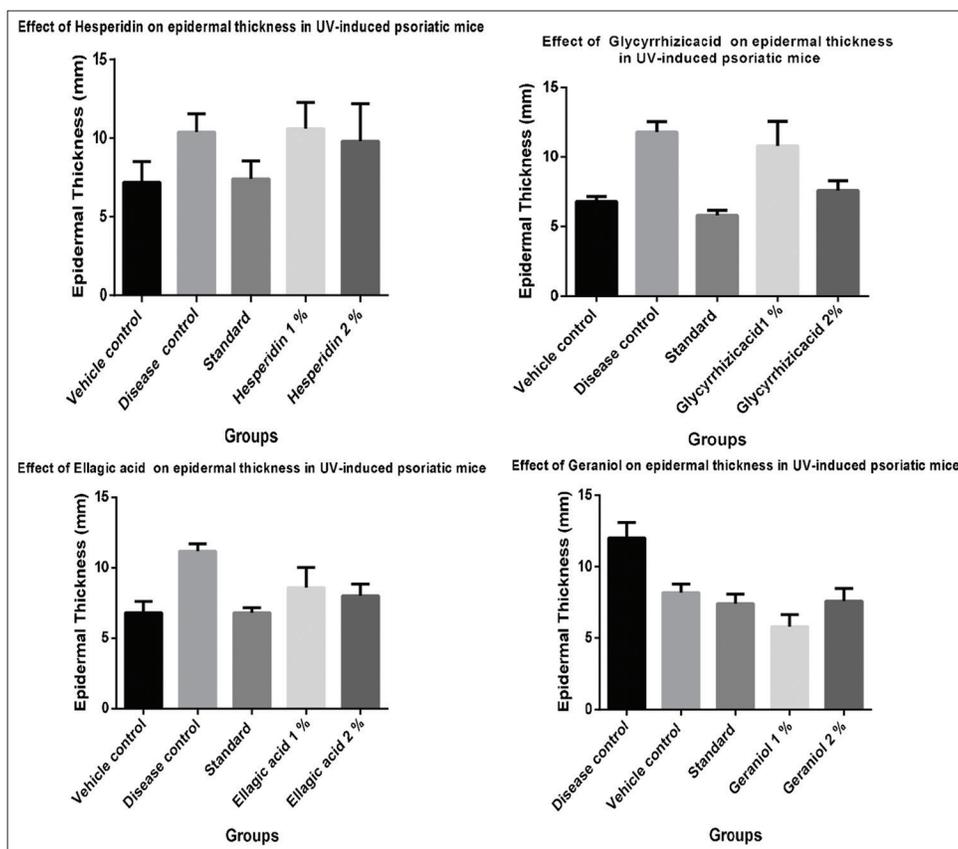


Figure 2: Effect of phytochemicals on epidermal thickness of mouse tail in UV-induced psoriatic animal.

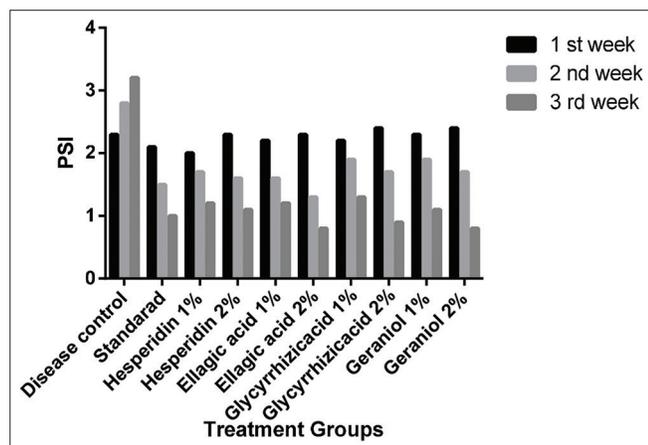


Figure 3: Effect of phytochemicals on Psoriasis Severity Index.

group, when compare to the disease-induced animal. It indicating that phytochemicals have an influence to retard the hyperproliferation of the keratinocytes that occur when the skin is exposed to UV radiation. The significant retention of the stratum granulosum is probably due to its ability to enhance the keratinisation process, which is a protective strategy adopted by the skin when exposed to penetrating radiation. Further, phytoconstituents produced useful

changes in the epidermis of the irradiated skin, showing its potential use in psoriasis treatment.

A natural polyphenols, recognised as potent antioxidants, are multifunctional molecules that can act as anti-inflammatory and antiproliferative agents through the modulation of multiple signalling pathways. This characteristic could be advantageous for the treatment of multicausal diseases caused by oxidative stress, including psoriasis. In an earlier work, Vijayalakshmi *et al.*<sup>[13]</sup> reported that the flavonoid quercetin showed significant reduction in epidermal thickness with respect to control in Perry's mouse tail model. Jadranka Skuric *et al.*<sup>[14]</sup> reported that the flavonoids from propolis offer some protection against psoriatic complications through their roles as inhibitors of inflammation and as free radicals scavengers on animal model psoriasis, induced by the UV induced. The observed anti-psoriatic activity may be through the inhibition of keratinocyte proliferation, which may be attributed to the antioxidant properties of selected phytoconstituents, especially geraniol, Glycyrrhizic acid and ellagic acid.

## CONCLUSION

The result of the study showed that 2% of geraniol, Glycyrrhizic acid and ellagic acid exhibited significant activity

on UV-induced psoriasis in rodents. The study implies that selected phytoconstituents are a promising research for further investigations to prove its anti-psoriatic activity.

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### Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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