

Efficacy and Safety of Cream Containing Dipotassium Glycyrrhizinate, *Vaccinium myrtillus*, Epigallocatechin Gallatyl Glucoside, and *Tamarindus indica* Compared with Triamcinolone Acetonide Cream in Eczema and Psoriasis

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Background: Topical corticosteroids are the main treatment in eczema and psoriasis. However, long-term use of corticosteroids causes unwanted adverse effects. Dipotassium glycyrrhizinate (DPG) HERB cream, containing DPG, *Vaccinium myrtillus*, epigallocatechin gallatyl glucoside, and *Tamarindus indica*, has an anti-inflammatory and antioxidant effect by inhibiting histamine release and proinflammatory cytokine production so a natural herbal cream is required for alternative treatment.

Objective: To evaluate the efficacy and safety of DPG-HERB.

Materials and Methods: The present study was a right-left, double-blinded, randomized clinical trial in participants with eczema or plaque psoriasis on both sides of the body. DPG-HERB was applied to the lesion on one side of the body, while 0.1% triamcinolone acetonide (TA) cream was applied to the lesion on the other side, twice daily for four weeks. Disease severity as eczema area and severity index (EASI) in eczema, and psoriasis area and severity index (PASI) in psoriasis, skin biophysics as corneometry and transepidermal water loss (TEWL), and clinical assessments as erythema, scale or excoriation, and lichenification or thickness, were evaluated at baseline, week 2 and week 4 after treatment. The dermatology life quality index (DLQI) was performed at baseline and week 4. Adverse effects were recorded during each visit.

Results: The evaluation of the 75 patients with 150 lesions in the present study, DPG-HERB and TA cream showed significant improvement in all the evaluated characteristics of eczema ($p < 0.05$), however, in psoriasis, both creams showed significant improvement in skin biophysics, PASI, scale, and thickness ($p < 0.05$), but DPG-HERB was less effective in decreasing erythema (DPG-HERB, $p = 0.31$ and TA, $p < 0.05$) and less improving TEWL compared with 0.1% TA cream (DPG-HERB, $p = 0.051$ and TA, $p < 0.05$). No side effects in the short-term period were reported in either group.

Conclusion: DPG-HERB is safe and efficacious in eczema, but less effective in psoriasis comparing to TA cream.

Keywords: Eczema; Plaque psoriasis; Dipotassium glycyrrhizinate acid

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Psoriasis vulgaris is the most common variant of psoriasis and presents as symmetrical, well-demarcated erythema extensor surfaces, nails, scalp, and trunk, manifested as silvery scales. The pathogenesis of plaque psoriasis is through immune-

mediated skin disease^(1,2). Eczema is chronic skin inflammation, which typically presents as dryness, erythema, and excoriation⁽³⁾. The lesion presents differently at various stages as vesicles, serous exudates, and lichenification. The pathogenesis of eczema is through skin barrier impairment that increases transepidermal water loss (TEWL) and develops skin inflammation⁽⁴⁾. Topical corticosteroids are the main therapeutic option in both skin diseases^(1,3). The mechanism of action comprises anti-inflammatory effects, anti-proliferation effects, and downstream signals of pro-inflammatory cytokines⁽¹⁾. However, side effects of long-term use of topical corticosteroids consist of skin atrophy, striae, telangiectasia, and hypothalamic-pituitary-adrenal axis and adrenal gland axis suppression⁽¹⁾.

Dipotassium glycyrrhizinate (DPG) HERB is

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a steroid-sparing cream composed of DPG from licorice, epigallocatechin gallatyl glucoside from green tea, *Tamarindus indica*, and *Vaccinium myrtillus*. DPG is an active ingredient that has an anti-inflammatory or antioxidant effect by inhibiting histamine release and proinflammatory cytokine production in mast cells. In addition, inhibition of phorbol ester-induced activation of nuclear factor kappa B (NF- κ B) is induced by epigallocatechin gallate to inhibit cyclooxygenase-2 (COX-2) - an anti-inflammatory cytokine⁽⁵⁾.

The present study postulated that DPG-HERB with anti-inflammatory or antioxidant effects might relieve inflammation and restore skin barrier function in eczema and psoriasis. The objective of the present study was to demonstrate the efficacy and safety of DPG-HERB compared with that of 0.1% triamcinolone acetonide (TA) cream in eczema and psoriasis.

Materials and Methods

Ethics and study design

The present study was a right-left, double-blinded, randomized clinical trial. The study was approved by the Institutional Review Board (IRB) of Panyanantaphikkhu Chonprathan Medical Center (EC019/61) and followed the Declaration of Helsinki. The present study was registered at www.thaiclinicaltrials.org with identification code TCTR20211025002. Informed consents were obtained from all participants.

Participants

Seventy-five healthy participants with 150 lesions, with chronic eczema or plaque psoriasis, diagnosed by the dermatologists, were enrolled by two assigned dermatologists from the outpatient service, Department of Medicine, Panyanantaphikkhu Chonprathan Medical Center between July 2019 and December 2021. The participants, aged 18 years or older, had chronic eczema or mild plaque psoriasis on both sides of trunk, the upper or lower extremities with body surface area involvement of less than 3%. Exclusion criteria were participants who had used topical corticosteroids in the previous two weeks or systemic immunosuppressive drugs in the previous four weeks, pregnant or lactating, and history of allergic reaction to the cream being studied.

Therapeutic protocol

The DPG-HERB cream (Sino Pharm Co., Ltd., Bangkok Thailand), containing 1% DPG, 0.1%

Vaccinium myrtillus, 1% epigallocatechin gallatyl glucoside, and 3% *Tamarindus indica*, and 0.1% TA cream were arranged in identical tubes with different codes (A and B). A technician (NY) who was not participating in the study, randomized the sides of the participants as either 'DPG-HERB-treated sides' or 'TA-treated sides', by using a computer-generated blocked design method. The participants and investigators were blinded to the type of cream. Both creams were white in color. All participants received two tubes of cream labeled 'A' and 'B', one for the right side and another for the left side. All participants received 30 grams of each cream. The fingertip unit (FTU) method was used when applying cream⁽⁶⁾. Participants used two to three FTUs for completing the treatment of all lesions twice a day for four weeks.

Clinical assessment

The primary outcome of disease severity for eczema area and severity index (EASI) in eczema and PASI in psoriasis, was determined at baseline, week 2, and week 4. The EASI score consists of redness, scale, lichenification, and excoriation ranging from 0 for absent to 3 for severe, whereas the PASI score is comprised of erythema, induration, and scale ranging from 0 for absent to 4 for very severe. The scores were weighed by the area of skin involvement over the trunk, upper or lower extremities.

The secondary outcomes were skin biophysics per corneometry and TEWL, clinical assessments per erythema, scale, lichenification and thickness, and dermatology life quality index (DLQI). All skin biophysics and clinical assessments were performed at baseline, week 2, and week 4. Corneometry and TEWL were used as markers of skin barrier function, measured by using Corneometer® CM825 (Courage and Khazaka Electronic GmbH, Köln, Germany) and Tewameter® TM300 (Courage and Khazaka Electronic GmbH), respectively, on the reference area, with a modified plastic template used to mark the site of measurement. The participants were allowed to rest for at least 20 minutes in a controlled temperature room at 20°C and 40% to 60% relative humidity, before the measurement. The symmetrical lesion on each side of the trunk, upper or lower extremities were selected and evaluated. The comparative photographs of clinical assessments for the presence of erythema, scale, lichenification or thickness using a four-point grading system with 0 for none, 1 for less than 25%, 2 for 25% to 50%, and 3 for more than 50% of the treated area, were evaluated by two blinded dermatologists (NC and JT).

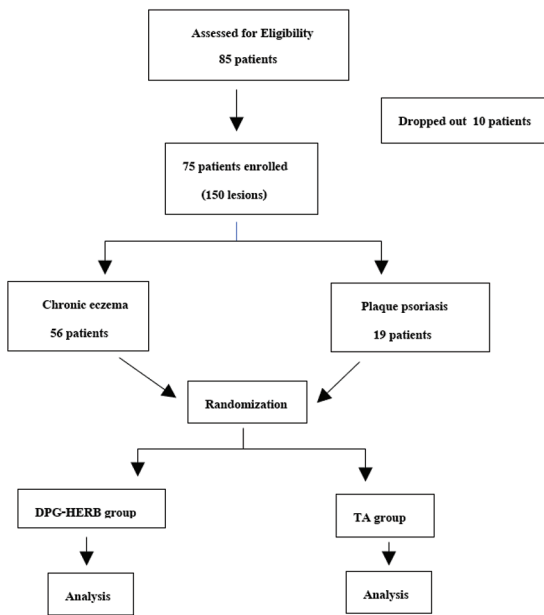


Figure 1. Flow chart of patient enrollment.

All digital photographs were taken using identical camera settings with a DSLR camera (Canon EOS 80D, Japan) at baseline, week 2, and week 4. The DLQI questionnaires were assessed by using the Patient Orientated Eczema Measure (POEM) to determine the severity of symptoms that had been recorded by participants before and after treatment, with 0 to 2 for clear or almost clear, 3 to 7 for mild, 8 to 16 for moderate, 17 to 24 for severe, and 25 to 28 for very severe. POEM was translated from English to Thai. The content was validated based on the index of item objective congruence (IOC) by three experts. Adverse events were recorded throughout the treatment.

Statistical analysis

Statistical analyses were performed with the SPSS Statistics, version 16.0 (SPSS Inc., Chicago, IL, USA). Repeated measures ANOVA and multiple comparison (Scheffe) were used to evaluate the severity of disease and the improvement of skin barrier function. A p-value of less than 0.05 was considered as significant.

Results

Seventy-five participants with 150 samples, including 33 females with 66 lesions or 44% and 42 males with 84 lesions or 56%, were enrolled in and completed the study in Figure 1. The age of the participants was 21 to 84 years with a mean age of

Table 1. Baseline characteristics (total n=150)

Characteristic	DPG-HERB-treated sides (n=75)	TA-treated sides (n=75)	p-value
Age (years); mean [SD]	53.7 [12.49]		
Sex; n (%)			
Male	42 (56.0)		
Female	33 (44.0)		
Type of skin disease; n (%)			
Chronic eczema	56 (74.7)		
• Dorsum of hand	10 (17.8)		
• Elbow	6 (10.7)		
• Trunk	8 (14.2)		
• Leg	12 (21.4)		
• Knee	5 (8.9)		
• Ankle	6 (10.7)		
• Dorsum of foot	7 (12.5)		
Plaque psoriasis	19 (25.3)		
• Arm	1 (5.2)		
• Elbow	3 (15.7)		
• Trunk	4 (21.0)		
• Leg	7 (36.8)		
• Knee	2 (10.5)		
• Dorsum of foot	2 (10.5)		
Corneometry levels; mean [SD]			
Chronic eczema	17.08 [13.9]	15.36 [10.42]	0.859
Plaque psoriasis	12.45 [11.4]	12.94 [10.03]	0.603
TEWL levels; mean [SD]			
Chronic eczema	35.18 [35.15]	30.96 [31.35]	0.130
Plaque psoriasis	28.02 [28.00]	29.59 [31.80]	0.991
Severity disease before treatment; mean [SD]			
EASI	1.35 [2.0]	1.35 [1.4]	0.549
PASI	1.82 [2.0]	1.91 [1.6]	0.451

DPG-HERB=cream containing dipotassium glycyrrhizinate, *Vaccinium myrtillus*, epigallocatechin gallate glucoside, and *Tamarindus indica*; TA=0.1% triamcinolone acetonide cream; TEWL=transepidermal water loss; EASI=eczema area and severity index; PASI=psoriasis area and severity index; SD=standard deviation

53.7 years old. At baseline, there was no statistically significant difference between disease severity, corneometry levels, and TEWL in the two groups. The demographic data are shown in Table 1.

At the end of the treatment of the DPG-HERB-treated sides, a significant reduction was observed in the EASI/PASI score in eczema and psoriasis ($p<0.001$ and $p=0.021$, respectively). Likewise, at the end of the treatment of the TA-treated sides, it was observed that the mean scores of EASI/PASI were significantly reduced in eczema and psoriasis ($p<0.001$ and $p=0.002$; respectively). The data are shown in Figure 2A-B.

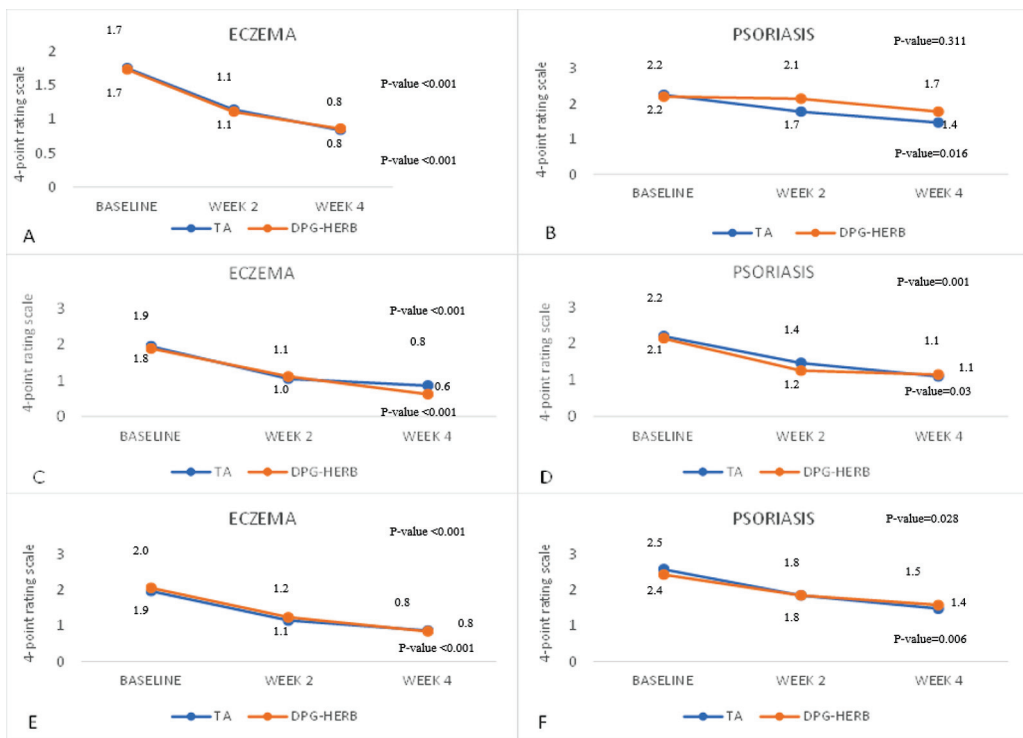


Figure 2. The 4-point rating scale of (A-B) erythema (C-D) excoriation/scale (E-F) lichenification/thickness in eczema and psoriasis at baseline, 2 and 4 weeks after treatment.

TA=0.1% triamcinolone acetonide cream; DPG-HERB=cream containing dipotassium glycyrrhizinate, *Vaccinium myrtillus*, epigallocatechin gallatyl glucoside, and *Tamarindus indica*

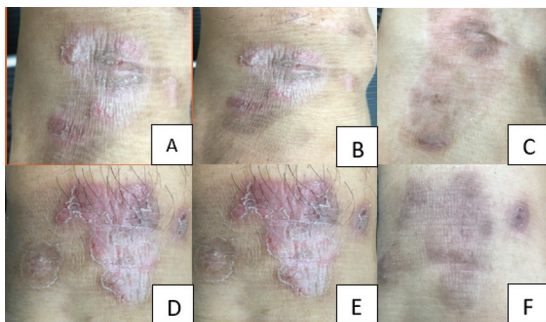


Figure 3. Global photography of patient with plaque psoriasis treated with DPG-HERB (A-C) and TA cream (D-F) at baseline, 2 weeks, and 4 weeks, respectively.

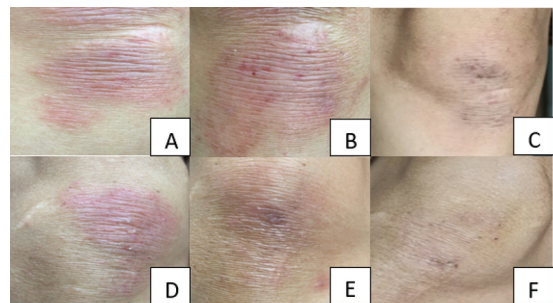


Figure 4. Global photography of patient with chronic eczema treated with DPG-HERB (A-C) and TA cream (D-F) at baseline, 2 weeks, and 4 weeks, respectively.

At the last visit of treatment, it was observed that the corneometry levels in DPG-HERB-treated sides had significantly increased from those of the baseline in eczema and psoriasis ($p<0.001$ and $p<0.001$, respectively) and in the TA-treated sides, it was observed that the mean score had significantly increased from that of the baseline in eczema and psoriasis ($p<0.001$ and $p=0.014$, respectively). The data are shown in Figure 2C-D and Table 2. This

was in accordance with the TEWL levels, which had continuously decreased from the baseline throughout the study (DPG-HERB-treated sides: $p<0.001$ and TA-treated sides, $p<0.001$ in eczema; and DPG-HERB-treated sides, $p=0.051$ and TA-treated sides: $p<0.001$ in psoriasis). The data are shown in Figure 2E-F.

In both creams, the mean score of all clinical assessments were significantly reduced after treatment

Table 2. Comparison of the skin biophysics and clinical assessments in both groups before and after treatment

	DPG-HERB treated-sides; mean (SD)			TA-treated sides; mean (SD)		
	Before	After	p-value	Before	After	p-value
Disease severity						
pEASI	1.3 (0.42)	0.6 (0.44)	<0.001	1.3 (0.38)	0.7 (0.43)	<0.001
pPASI	1.8 (0.93)	1.3 (0.94)	0.001	1.9 (1.09)	1.2 (0.83)	0.002
Skin biophysics						
Corneometry levels						
• Eczema	17.0 (11.48)	31.2 (17.29)	<0.001	15.3 (10.50)	27.1 (14.28)	<0.001
• Psoriasis	12.4 (7.99)	23.8 (12.55)	<0.001	12.9 (7.55)	24.3 (20.26)	0.014
TEWL levels						
• Eczema	35.1 (15.01)	21.0 (9.31)	<0.001	30.9 (11.9)	22.3 (9.90)	<0.001
• Psoriasis	28.0 (12.45)	21.0 (12.30)	0.051	29.5 (12.64)	21.4 (9.86)	<0.001
Clinical assessments						
• Erythema						
Eczema	1.70 (0.88)	0.80 (0.81)	<0.001	1.70 (0.87)	0.80 (0.82)	<0.001
Psoriasis	2.20 (0.18)	1.70 (0.23)	0.311	2.20 (0.18)	1.40 (0.24)	0.016
• Excoriation/scale						
Eczema	1.80 (0.94)	0.62 (0.70)	<0.001	1.90 (0.94)	0.80 (0.74)	<0.001
Psoriasis	2.10 (0.20)	1.10 (0.19)	0.003	2.20 (0.18)	1.10 (0.16)	0.001
• Lichenification/thickness						
Eczema	2.00 (0.86)	0.80 (0.78)	<0.001	1.90 (0.83)	0.80 (0.81)	<0.001
Psoriasis	2.40 (0.19)	1.50 (0.25)	0.028	2.50 (0.22)	1.40 (0.24)	0.006

DPG-HERB=cream containing dipotassium glycyrrhizinate, *Vaccinium myrtillius*, epigallocatechin gallatyl glucoside, and *Tamarindus indica*; TA=0.1% triamcinolone acetonide cream; pEASI=partial eczema area and severity index; pPASI=partial psoriasis area and severity index; TEWL=transepidermal water loss; SD=standard deviation

in eczema and psoriasis ($p<0.05$) (Figure 3, 4) but the effectiveness of 0.1% TA cream was superior to that of DPG-HERB in decreasing erythema ($p<0.05$ and $p=0.31$, respectively). The data are shown in Figure 5 and Table 2. DLQI showed improvement in both groups ($p<0.001$). In DPG-HERB-treated sides, the PGA at four weeks after treatment showed that 50% and 30% of participants had excellent to complete improvement in eczema and psoriasis, respectively, while in TA-treated sides, the PGA at four weeks after treatment showed that 40% and 30% of participants had excellent to complete improvement in eczema and psoriasis, respectively. No side effects were reported or observed in either group.

Discussion

Psoriasis is an immune-mediated disease that can affect long-term outcomes, such as those of cardiovascular disease, joints, and quality of life, because of chronic activation of the immune system⁽²⁾. Pathways and key transcription factors have been associated with psoriasis, such as the NF- κ B signaling pathway, cyclic adenosine monophosphate

(cAMP) pathway, and T-helper (Th) 1, 17, and 22 cells, leading to the production of inflammatory cytokines^(2,7). In eczema, the pathophysiology involves Th2 immune dysregulation, skin barrier dysfunction, and skin microbiome abnormalities. Th2 cytokines, including mediated interleukins (IL) 4, 13, 31, directly stimulate sensory nerves and promotes itching⁽⁸⁾. The natural history of relapsing-remitting disease results in adverse effects from long-term use of corticosteroids^(1,4). Herbal extract cream is an alternative treatment for promoting anti-inflammatory effects.

DPG-HERB has a main component called DPG, extracted from licorice, which has been used for inflammatory skin conditions such as psoriasis due to its anti-inflammatory effect and immunoregulatory activity through mechanisms such as prohibiting vascular leakage induced by vasoactive agents, preventing NF- κ B signaling pathways in keratinocytes, and reducing the production of eotaxin-1, which is an eosinophil chemoattractant, a main component of Th2-type disease, such as AD⁽⁹⁾. Other ingredients are epigallocatechin gallatyl glucoside, extracted from green tea, which

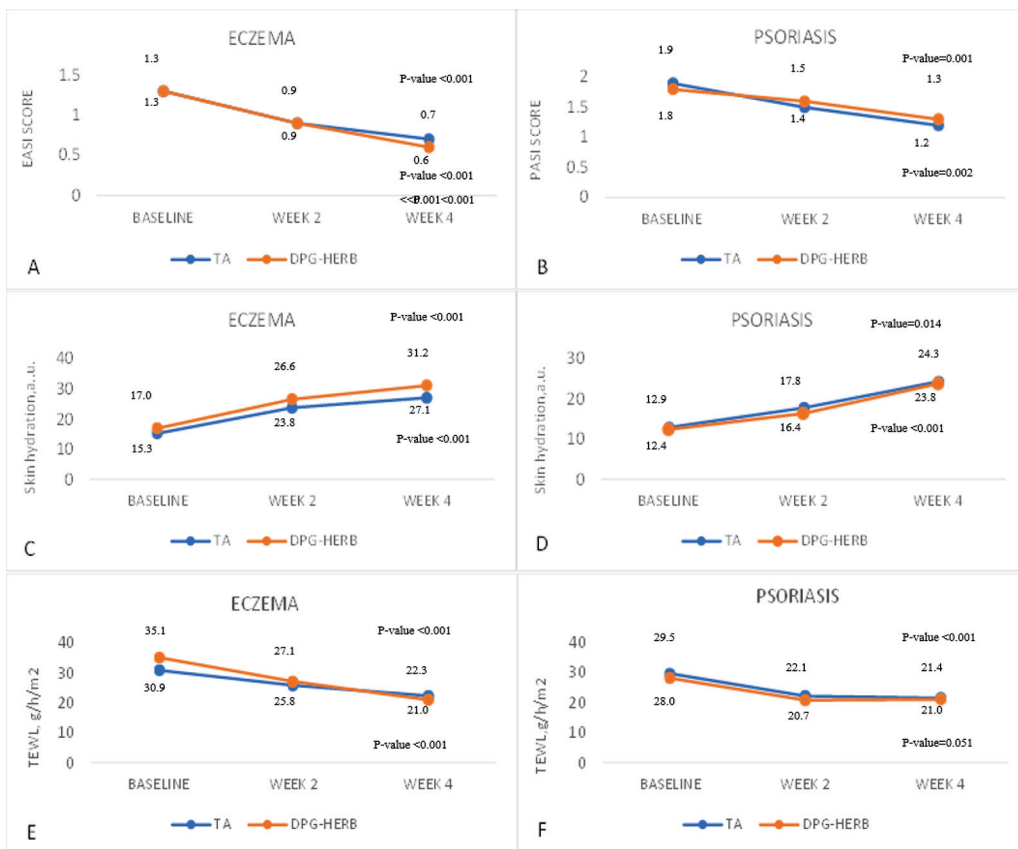


Figure 5. (A-B) Severity disease score, (C-D) Corneometry level, (E-F) Transepidermal loss level at baseline, 2 and 4 weeks after treatment in eczema and psoriasis.

TA=0.1% triamcinolone acetonide cream; DPG-HERB=cream containing dipotassium glycyrrhizinate, *Vaccinium myrtillus*, epigallocatechin gallatyl glucoside, and *Tamarindus indica*; pEASI=partial eczema area and severity index; pPASI=partial psoriasis area and severity index

has antioxidant and anti-inflammatory effects and suppresses NF- κ B and activator protein-1 (AP-1) pathways⁽¹⁰⁾. *Tamarindus indica* has an anti-inflammatory effect via inhibition of leukotriene biosynthesis, COX-2, and NF- κ B⁽¹¹⁾. The anthocyanin extracted from *Vaccinium myrtillus* significantly inhibits mast cell degranulation. This mechanism is associated with an antipruritic effect⁽¹²⁾.

In a previous study, Yu et al. (2017) showed that the compound glycyrrhizin combined with topical corticosteroids enhanced clinical improvement in plaque psoriasis via the inhibition of the NF- κ B signaling pathway in keratinocytes⁽⁹⁾. Kim et al. showed that DPG extracted from licorice could regulate expression of AD-related genes in both IL-4 and IL-13-stimulated epidermal keratinocytes and decrease pro-inflammatory cytokine production in AD-like conditions in a human skin equivalent model⁽¹⁰⁾. The study of Xiong et al. showed that glycyrrhizin could be applied as an anti-psoriasis

drug as it has been shown to inhibit TNF- α -induced activation of the NF- κ B signaling pathway in vitro and in vivo⁽¹³⁾.

The present study demonstrated that there was no statistically significant difference in the efficacy between DPG-HERB and 0.1% TA cream in reducing disease severity, erythema, scale, lichenification, and TEWL, and improving skin barrier function in eczema. However, in psoriasis, DPG-HERB and 0.1% TA cream could improve skin barrier function, disease severity, scale, and thickness but the effectiveness of 0.1% TA cream was found to be superior in decreasing TEWL and erythema. The efficacy of DPG-HERB did not differ from that of 0.1% TA cream in eczema, but DPG-HERB was less effective in comparison to 0.1% TA in psoriasis. These findings reflected the anti-inflammatory effect of DPG-HERB, which was concordant with a previous in-vitro study by Teelucksingh et al. who found that glycyrrhetic acid is a potent inhibitor

of the enzyme 11 β -hydroxysteroid dehydrogenase, which is found in inflammatory skin diseases such as psoriasis and eczema. The anti-inflammatory effect of glycyrrhetic acid is equivalent to hydrocortisone⁽¹⁴⁾. Similar to the present study, the effectiveness of DPG-HERB has less equivalent potency of corticosteroids compared with 0.1% TA cream. This may be due to the lower capability of DPG-HERB in penetrating deep to thick plaque in psoriasis.

A limitation of the present study was the inconvenience of recruiting the participants during the COVID-19 situation in Thailand.

In conclusion, the present study demonstrated the efficacy and safety of using DPG-HERB in eczema and psoriasis. However, the study period is short, so the long-term side effects should be monitored, and further studies are needed to evaluate the combination of DPG-HERB with penetration enhancers in psoriasis and other inflammatory skin diseases.

What is already known on this topic?

In a previous study, Yu et al. (2017) showed that the compound glycyrrhizin combined with topical corticosteroids enhanced clinical improvement in plaque psoriasis⁽⁹⁾. However, there is no clinical study comparing glycyrrhizin and 0.1% TA cream in eczema and psoriasis.

What this study adds?

The efficacy of DPG-HERB did not differ from that of 0.1% TA cream in eczema, but DPG-HERB was less effective in comparison to 0.1% TA in psoriasis. Thereby, DPG-HERB is an alternative treatment for eczema and psoriasis.

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Conflicts of interest

The authors reported no conflicts of interest in this study.

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