A randomized, double-blind clinical trial on the efficacy and safety of turmeric 1% cream in the treatment of plaque-type psoriasis in adults

Bryan Edgar Guevara, MD[1] Elisa Rae Coo, MD[2], Mary Jo Christine Bunagan, MD[1]

Background: Turmeric demonstrated anti-inflammatory properties in laboratory and clinical studies that suggest its usefulness in psoriasis. This is the first randomized controlled trial comparing the efficacy and safety of turmeric 1% cream to clobetasol propionate 0.05% cream in the treatment of plaque-type psoriasis.

Objectives: To determine the efficacy and safety of turmeric 1% cream versus that of clobetasol propionate 0.05% cream in the treatment of plaque-type psoriasis.

Methods: This was a randomized, double-blind clinical trial to determine the proportion of patients with clinical remission. Secondary outcomes namely mean PASI and pruritus scores per visit, time to remission and incidence of adverse effects were also determined.

Results: Fifty-nine patients were randomized into two groups: a turmeric (n=30) and a clobetasol (n=29) group. After four weeks of treatment, there was no significant difference (p=0.36) in the proportions of patients with clinical remission in the turmeric group (5/20, 25%) and the clobetasol group (8/23, 35%) (RR 1.15, 95% CI 0.78-1.70). The average time to achieve clinical remission was 4 weeks in the turmeric group and 3.38 ± 1.06 weeks in the clobetasol group (p=0.07). There was no significant difference in post-treatment mean PASI scores in turmeric (8.77 ± 5.71) and clobetasol (7.26 ± 6.04) groups (p=0.40). Post-treatment mean pruritus scores in turmeric (6.9 ± 2.83) and clobetasol (5.83 ± 3.87) groups (p=0.30) were also statistically comparable. Two patients in the clobetasol group developed folliculitis.

Conclusion: Turmeric 1% cream demonstrated comparable efficacy and safety with clobetasol 0.05% cream in the treatment of mild to moderate plaque-type psoriasis.

Keywords: Turmeric, Plaque-type Psoriasis, Clinical Trial

[1] **Consultant, Department of Dermatology, Southern Philippines Medical Center**
[2] **Graduate, Department of Dermatology, Southern Philippines Medical Center**

Source of funding: none
Conflict of interest: none
Corresponding author: Bryan Edgar Guevara MD, Southern Philippines Medical Center, Davao City
Bry0529@yahoo.com

INTRODUCTION

Psoriasis is a chronic, debilitating disease which affects roughly 2% of the world population.[1] The Philippine Dermatological Society (PDS) ranked psoriasis as the 3rd most commonly diagnosed skin disease in 2011.[2] Topical steroids continue to be the standard first line treatment for mild to moderate plaque-type psoriasis. The long-term treatment required and the prohibitive adverse effects of prolonged steroid use make it relevant to find an alternative medication for this debilitating condition.

Turmeric, or *Curcuma longa*, is a perennial herb of the *Zingiberaceae* (ginger) family that has anti-inflammatory properties.[3] Curcumin is a polyphenol that has been extensively studied for its therapeutic effects, evident in modulating several molecular targets and inhibiting transcription factors (NFκB), enzymes (COX-1,-2 and LOX), and cytokines (TNF, IL-1 and IL-6) in in-vitro and in-vivo studies.[4,5] A study has also shown that topical curcumin can control psoriasis through the suppression of phosphorylase kinase activity.[6] These anti-inflammatory properties may control an immunologically-mediated disease such as psoriasis. Turmeric appears to be non-toxic to humans, and the United States Food and Drug Administration (FDA) has categorized curcumin as 'generally recognized as safe' (GRAS).[7] Curcumin has been marketed in several forms such as tablets, drinks, ointments, soaps and other cosmetics with no reported side effects.[8]

This randomized controlled trial compared the efficacy and safety of turmeric 1% cream to clobetasol propionate 0.05% cream in the treatment of plaque-type psoriasis.

OBJECTIVES

Overall, the efficacy and safety of turmeric 1% cream versus that of clobetasol propionate 0.05% cream in the treatment of plaque-type psoriasis was determined in this study. Specifically, the following outcomes were determined in both groups: the proportion of patients with clinical remission, mean time to achieve clinical remission, mean PASI scores per visit, mean pruritus score per visit, and the incidence of adverse events.

METHODOLOGY

Patients and study design

This study was a randomized, double-blind, controlled trial conducted at the the dermatology outpatient department of a tertiary dermatology referral center from August 2015 to July 2016. The hospital's review board approved the trial protocol before the study was started. Informed consent from all participants was likewise secured prior to treatment. This trial was carried out in accordance with the Declaration of Helsinki principles, Good Clinical Practice (GCP) guidelines, and local regulations. Prior to conduct, ethical review was obtained and registration for this trial was made with the Philippine Food and Drug Administration (FDA) Health Research Registry (Registry ID: PHRR12005-001100).

Adult psoriasis patients with a PASI score of 30 were included regardless of disease duration.[9] Patients who applied topical medications for the past 2 weeks and patients who have taken systemic medications for the past 4 weeks for psoriasis were excluded from the study.

Materials

Both turmeric 1% cream and clobetasol propionate 0.05% cream were prepared by a local pharmaceutical company. The appearance, color, consistency and smell were similar in both groups and were repackaged and coded (A or B) by a pharmacist into uniform 20-gram plastic jars (Figure 1).

Clobetasol 0.05% and turmeric 1% creams, similar in physical properties, were manufactured by a local GMP-compliant manufacturer and were packaged similarly by a pharmacist. Turmeric 1% cream was shown by Heng et al. to have anti-psoriatic activity.[6]

Figure 1. Turmeric 1% cream (A) and Clobetasol 0.05% cream (B).

Randomization, treatment allocation, and blinding

Randomization was done electronically. Treatment assignment and end-point assessment were done by independent physicians who were not aware of the treatment being administered.

Interventions

Patients were instructed to apply *their assigned cream to* all involved body surfaces twice daily for four weeks*. They were each given a measuring spoon*

equivalent to 0.25 grams, and were advised to use one spoonful of medication for every 1% body surface area involved. Patients were instructed to apply the medications using the fingertip unit (FTU). The jars were weighed at each visit to ensure adequate use.

Outcome measures

The patients were evaluated at baseline, 1, 2, 3 and 4 weeks by the primary investigator. The primary endpoint of the study was the proportion of patients who demonstrated clinical remission. Secondary endpoints include mean PASI score per visit, mean time to achieve clinical remission, mean pruritus score per visit, and incidence of adverse effects. The study endpoints and digital photographs were obtained at every visit.

The clinical severity of psoriasis was measured using the Psoriasis Area and Severity Index (PASI) score.[11] After determining the PASI scores, patients were stratified based on the percentage decrease of PASI: 'complete response' when the PASI score at week 4 was 0; 'marked response' when the PASI score decreased ≥ 75% from the baseline; 'moderate response' when the PASI score decreased by 50 to 74% from the baseline; 'slight response' when the PASI score decreased <50% from the baseline; and 'no response' when the lesions will show no change after the end of therapy. The clinical findings of 'complete response' and 'marked response' will be interpreted as clinical remission. Findings of 'moderate response', 'slight response', and 'no response' will be interpreted as treatment failures similar to other studies.[11,12]

The Pruritus score was evaluated using the 5-D score, which is a multidimensional questionnaire designed as outcome measures in clinical trials and a reliable and validated tool to use in patients with psoriasis vulgaris.[22] The sum of the tallied distribution domain is sorted into five scoring bins: sum of 0-2= score 1, sum of 3–5 = score of 2, sum of 6–10 = score of 3, sum of 11–13 = score of 4, and sum of 14–16 = score of 5.[13]

Stopping guidelines

The study was stopped in patients who experienced a "flare" of psoriasis, defined as an episode requiring an escalation of treatment (necessitating other oral/topical medications). Appropriate rescue treatment and monitoring were done. These patients were considered as withdrawals from the study. Those who did not comply to the twice-a-day application of the test creams, or those who used other medications were also withdrawn from the study. Dropouts were defined as those who did not follow up within two weeks and whose outcome was unknown by the end of the study period.

Sample Size Computation

The sample size was calculated accepting a power of 80%, with a two-sided alpha of 0.05, using the formula for computing the difference between two proportions. The projected success rate (those who will have remission) for clobetasol was set at 96% and the assumed success rate for turmeric was at 66%, based on a success rate of the treatment arm in another study.[12] Calculations indicated that 26 patients in each study arm were needed (80% power, 5% level of significance). We aimed to recruit 59 patients to allow for a 15% dropout rate.

Data processing and analysis

To determine if the groups were significantly different in their demographic characteristics, the student's t-test was used to analyze continuous variables, while the Pearson chi-squared test was used for categorical data. The Pearson chi-squared test was used to estimate differences in proportions of patients achieving clinical remission or patients achieving PASI 75, as previously defined. The student's t-test was used to compare the difference in PASI scores, time to achieve clinical remission, and pruritus severity scores, while the Pearson chi-squared test was used to compare the proportion of patients who experienced adverse reactions between groups. Test results with p values below 0.05 were regarded as statistically significant.

To measure the association between treatment and remission, treatment effects such as relative risk (RR), RR reduction (RRR), absolute risk reduction (ARR) and number needed to treat (NNT) were computed, and 95% confidence intervals (CI) were determined. Statistical analyses were done using Open Epi downloaded version.

Two types of analysis— (1) an intention-to–treat (ITT) analysis, which includes all randomized patients in the groups to which they were randomly assigned regardless of the treatment they actually received and subsequent withdrawal from treatment or deviation from the protocol, and (2) a per protocol analysis, which excluded dropouts and considered only the patients who have completed the study— were done for this study.

RESULTS

Study population

Of the 65 participants screened, 59 met the entry criteria and were randomized to treatment (turmeric, n=30) and control (clobetasol, n=29) groups. Of these patients, 13 were considered as dropouts due to non-attendance at scheduled visits. There were three withdrawals (use of other forms of medication) (Figure 2). There were no statistical differences in the number of dropouts and withdrawals between the two groups (p = 0.219). The baseline characteristics of the study population are summarized in Table 1. No statistically significant differences were noted between the two groups based on age, sex, baseline PASI, baseline pruritus, duration of illness, and previous treatment.

Clinical effects

Patients in both groups demonstrated a decrease in PASI scores from baseline. However, patients in the clobetasol group showed significantly lower mean PASI scores during the 1st (p=0.04), 2nd (p=0.009), and 3rd (p=0.02) weeks of therapy. There was no significant difference in post-treatment mean PASI scores in turmeric (8.77 ± 5.71) and clobetasol (7.26 ± 6.04) groups (p=0.40).

Twenty-five (25%) percent of patients experienced remission in the turmeric group as compared to 35% of patients in the clobetasol group (p-value 0.36) (Table 2). Table 2 shows the clinical outcomes based on improvement in PASI scores. The mean remission time in the turmeric group was 4 ± 0 weeks, while the average time to remission in the clobetasol group was 3.38 ± 1.06 weeks (p=0.07)

Computation of the relative risk suggests a 15% higher risk of remission in the clobetasol group than in the turmeric group (RR 1.15, 95% CI 0.78-1.70). The 95% confidence interval suggests that treatment with clobetasol may lead to an increase of 70% in the chance of remission and to a decrease of 22% in the risk of remission. However, because the confidence interval includes 1, there is no evidence that turmeric therapy results in lower chance of remission as compared to clobetasol therapy. The NNT revealed that 10 patients were required to be treated with turmeric for 4 weeks to demonstrate remission. Sensitivity case analysis (intention to treat analysis using worst case scenario) showed an RR of 1.15 (95% CI 0.87-1.51), which signifies that the main analysis (per protocol analysis) was robust (Table 3).

Patients in both groups also demonstrated a decrease in pruritus scores from baseline (Figure 4). A significant difference was only noted during week two (p=0.02). There was no significant difference in the post-treatment mean pruritus scores between turmeric (6.9 ± 2.83) and clobetasol (5.83 ± 3.87) groups (p=0.30).

There were no adverse effects in the turmeric group, but two patients in the clobetasol group experienced folliculitis (p-value 0.998).

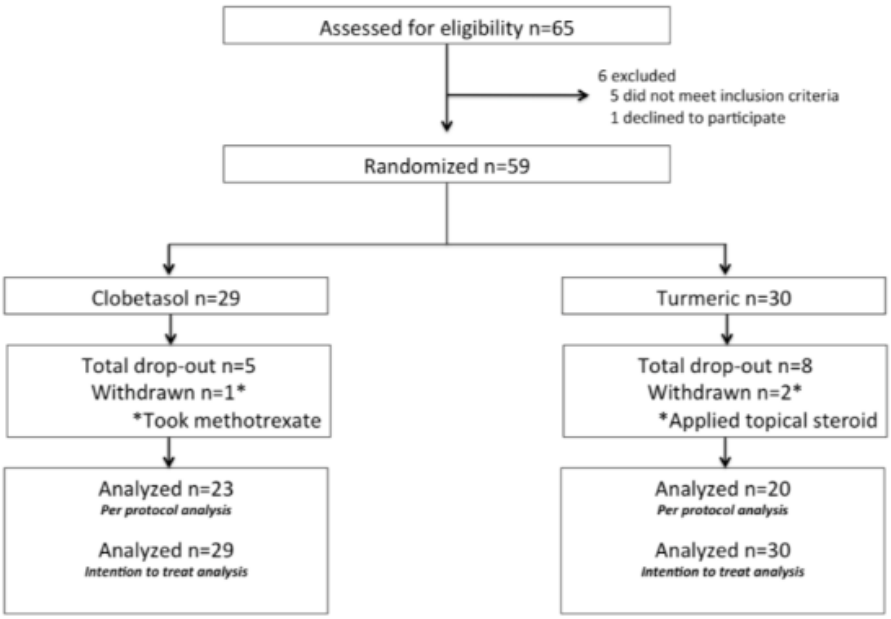


Figure 2. Screening, randomization, and analysis of patients in the study.

Table 1. Baseline demographic data

Characteristic	Turmeric group	Clobetasol group	p- value
Age ± SD	46.2 ± 16.82	44.93 ± 15.89	0.994
Sex, n (%)			
Male	15(50%)	19(66%)	0..228
Female	15(50%)	10(34%)	
Baseline PASI ± SD	17.72 ± 8.45	15.7 ± 9.29	0.288
Baseline Pruritus ± SD	12.62 ± 3.2	12.69 ± 2.99	0.680
Duration of Illness ± SD	74.83 ± 74.82	68.66 ± 74.44	0.394
Previous treatment, n (%)			
With Previous treatment	29(97%)	27(93%)	0.533
No previous treatment	1(3%)	2(7%)	

PASI - Psoriasis Area and Severity Index (PASI); SD - standard deviation

Table 2. Clinical outcomes based on improvement in PASI scores

	Clinical remission (n, %)		Clinical failure (n, %)		
	Complete response	***Marked response***	***Moderate response***	***Slight response***	***No response***
Turmeric	0 (0%)	5 (25%)	7 (35%)	8 (40%)	0 (0%)
Clobetasol	3 (13%)	5 (22%)	6 (26%)	6 (26%)	3 (13%)

Table 3. Clinical outcomes based on clinical remission/failure.

	Per protocol analysis		Intention to treat analysis	
	***Clinical remission* (n, %)**	***Clinical Failure* (n, %)**	***Clinical Remission* (n, %)**	***Clinical Failure* (n, %)**
Turmeric	5/20 (25%)	15/20 (75%)	5/30 (17%)	25/30 (83%)
Clobetasol	8/23 (35%)	15/23 (65%)	8/29 (30%)	21/29 (70%)

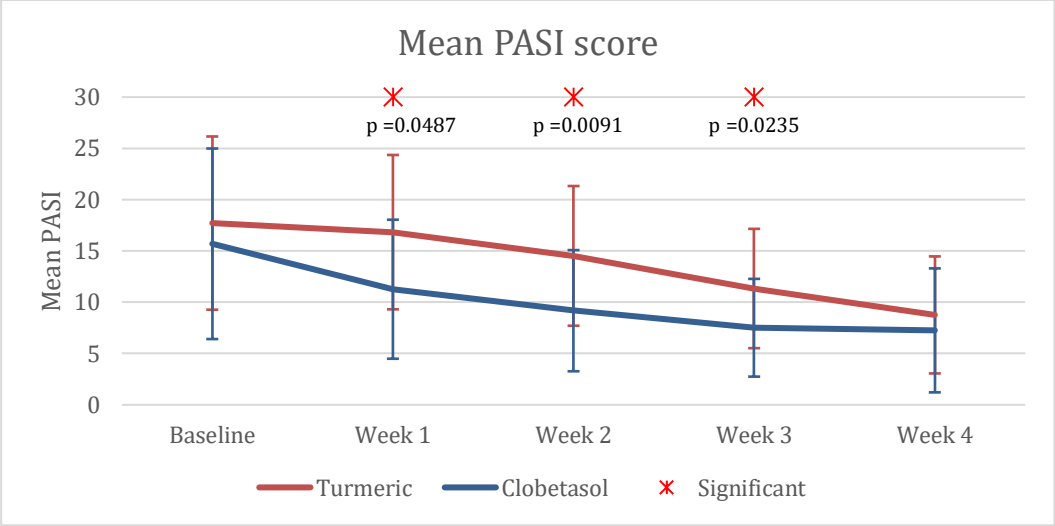


Figure 3. Decrease of PASI scores of turmeric and clobetasol groups throughout treatment.

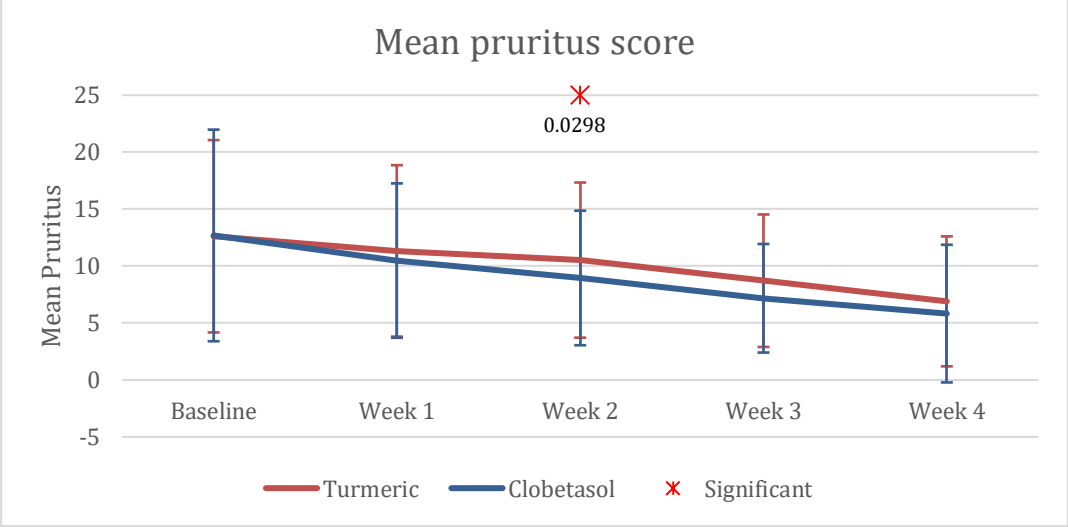


Figure 4. Decrease in pruritus scores of turmeric and clobetasol groups throughout treatment.

DISCUSSION

Our results have shown that treatment of plaque-type psoriasis with turmeric 1% cream and clobetasol propionate 0.05% cream were not significantly different based on the proportions of patients who experienced remission, time to remission, post-treatment PASI and pruritus scores, and the incidence of adverse effects. The beneficial effect of turmeric may be attributed to the anti-inflammatory properties of its active ingredient curcumin (diferuloylmethane).[14] Curcumin has been shown to modulate pro-inflammatory cytokines (tumor necrosis factor [TNF]-α, interleukin [IL]-1β, IL-6), enzymes, transcription factors (NF–κB), phosphorylase kinase (PhK), and oxidative stress in laboratory and clinical studies.[3-6,14-16] The abovementioned inflammatory mediators play a significant role in the pathogenesis of psoriasis. Hence, curcumin through its anti-inflammatory actions, may provide clinical remission (Figure 6).

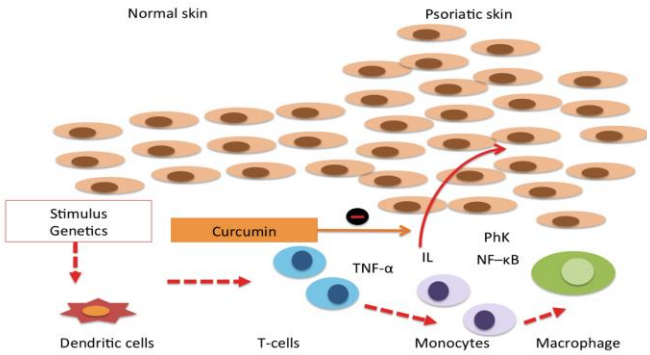


Figure 6. Possible mechanism of action of curcumin in psoriasis vulgaris. TNF- α, Tumor necrosis factor-α; IL, interleukin; PhK, phosphorylase kinase; NF- κB, NF- κ, kappaB.

Treatment with turmeric has a slower onset of action compared to clobetasol as evidenced by significantly lower PASI scores in the latter during the first three weeks of the study. Yet, the post-treatment PASI scores of both groups were comparable. The faster onset of action of clobetasol may be due to its ability to induce vasoconstriction, being a class 1, superpotent topical steroid.[26] This potency, however, leads to 2- to 4-week limitation of its use due to its risk of both cutaneous effects and systemic absorption.[17]

A decrease in pruritus score was seen in both groups. This is relevant because pruritus is observed in up to 90% of patients with psoriasis, and is reported to be the most bothersome symptom.[18-20] In addition to inflammation, an important mechanism of pruritus in psoriasis is the abnormal activation of the opioid receptors. Curcumin has been demonstrated to mediate anti-pruritic effects via mu and delta opioid receptors.[21,22] Furthermore, transient receptor potential vanilloid receptor-1 (TRPV 1), a mediator of histamine-induced itching, has also been inhibited by curcumin in in vitro studies.[23,24]

Although patients from both groups revealed improvement in PASI scores throughout treatment, less than half of the patients in both groups experienced clinical remission after a month of treatment. A longer treatment period might be needed for these topical medications to demonstrate higher remission rates. Similar to other anti-psoriatic medications, these require longer periods of use to produce clinical remission. For example, Biologics, which are newer, more effective but expensive psoriasis treatments, still require treatment duration of 8 to 16 weeks to achieve PASI 75 rates based on systematic reviews and meta-analyses.[25]

This study was conducted among adult patients diagnosed with plaque-type psoriasis with diverse demographic characteristics, and with clinical profiles that cover a wide range of previous treatment use and duration of illness. The results of this study may be applicable to most adult patients diagnosed with uncomplicated, localized plaque-type psoriasis with no co-morbid systemic illness. The efficacy and safety profile of turmeric cream makes it useful as monotherapy for patients who cannot tolerate or have contraindications for steroid use, or as a steroid-sparing agent during steroid rest periods.

One limitation of this study is that we conducted our research on adult psoriatic patients only. The safety profile of turmeric may indicate its use for pediatric patients who may be more susceptible to the adverse effects of steroids. As mentioned, it appears that the one-month duration of the study limited the maximal efficacy of both drugs as seen in the relatively low remission rates of both groups compared to other studies. We did not stratify patients to mild, moderate, and severe based on PASI scores, which would have helped in delineating the effects of the treatments based on clinical severity and then identifying what subset of patients the treatments are best used for. A larger sample size is also recommended in future studies to increase the precision of detecting treatment effects.

In conclusion, among adult patients diagnosed with mild to moderate plaque-type psoriasis, the topical application of turmeric 1% cream for four weeks was comparable to that of clobetasol propionate 0.05% cream based on efficacy and safety outcome measures.

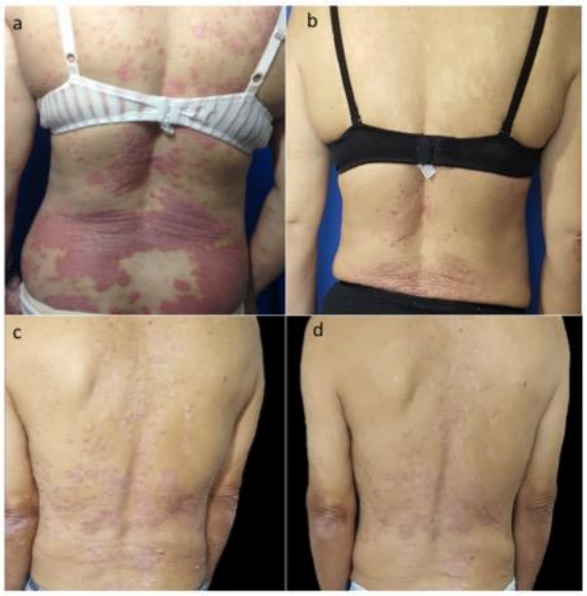
Acknowledgment

The authors would like to thank Dr. Mara Evangelista-Huber for her writing assistance, technical editing, and proofreading.

REFERENCES

1. Mrowietz U, Kragballe K, Reich K, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. Arch Dermatol Res. 2011;303:1–10.
2. Philippine Dermatological Society (PDS)- Health Information System. Most Common Skin Diseases, 2011.
3. Remadevi R, Surendran E, Kimura T. Turmeric in Traditional medicine. In Turmeric: the genus Curcuma. Ravindran PN, NirmalBabu K, Sivaraman K. Eds. CRC Press: Boca Raton, London,New York. 2007, pp. 409-436.
4. Aggarwal BB, Kunnumakkara AB, Harikumar KB, Tharakan ST, Sung B, Anand P. Potential of spice-derived phytochemicals for cancer prevention. Planta Med., 2008;74:1560-1569.
5. Funk JL, Frye JB, Oyarzo JN, Kuscuoglu N, Wilson J, McCaffrey G, et al. Efficacy and mechanism of action of turmeric supplements in the treatment of experimental arthritis. Arthritis Rheum. 2006;54:3452-3464.
6. Heng MC, Song MK, Harker J, Heng MK. Drug-induced suppression of phosphorylase kinase activity correlates with resolution of psoriasis as assessed by clinical, histological and immunohistochemical parameters. Br J Dermatol. 2000;143(5):937–949.
7. United States Food and Drug Agency (US FDA). http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/default.html
8. Goel A, Jhurani S, Aggarwal BB. Multi-targeted therapy by curcumin: how spicy is it? Mol Nutr Food Res. 2008;52(9):1010–1030.
9. Wen ZH, Xuan ML, Yan YH, Li XY, Yao DN, Li G et al. Chinese medicine combined with calcipotriol betamethasone and calcipotriol ointment for Psoriasis vulgaris (CMCBCOP): study protocol for a randomized controlled trial. Trials. 2014; 15:294.
10. Long C, Finlay A, et al. The finger-tip unit--a new practical measure. Clinical and Experimental Dermatology. 1991;16(6):444-7.
11. Oakley, A. Psoriasis Area and Severity Index (PASI) score. 2011. Retrieved from http://www.dermnetnz.org/scaly/pasi.html
12. Tangtatco JA, Guillano V. A prospective, randomized, double-blind, comparative study on the efficacy and safety of capsaicin 0.05% cream versus clobetasol propionate 0.05% cream in the treatment of mild to moderate plaque type psoriasis. [unpublished]. 2014
13. Elman, S. et al. (2010). The 5-D itch scale: a new measure of pruritus. British Journal of Dermatology, 162. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2875190/#!po=17.8571
14. Gupta S, Patchva S, Aggarwal B. Therapeutic roles of curcumin: Lessons learned from clinical trials. AAPS J. 2013;15(1):195-218.
15. Dhillon N, Aggarwal BB, Newman RA, Wolff RA, Kunnumakkara AB, Abbruzzese JL, et al. Phase II trial of curcumin in patients with advanced pancreatic cancer. Clin Cancer Res. 2008;14(14):4491–4499.
16. Usharani P, Mateen AA, Naidu MU, Raju YS, Chandra N. Effect of NCB-02, atorvastatin and placebo on endothelial function, oxidative stress and inflammatory markers in patients with type 2 diabetes mellitus: a randomized, parallel-group, placebo-controlled, 8-week study. Drugs R D. 2008; 9(4):243–250.
17. Cornell RC, Stoughton RB. Correlation of the vasoconstriction assay and clinical activity in psoriasis. Arch Dermatol 1985;121:63-7.
18. Szepietowski JC, Reich A, Wiśnicka B. Itching in patients suffering from psoriasis. *Acta Dermatovenerologica Croatica*. 2002;10(4):221–226.
19. Yosipovitch G, Goon A, Wee J, Chan YH, Goh CL. The prevalence and clinical characteristics of pruritus among patients with extensive psoriasis. *British Journal of Dermatology*. 2000;143(5):969–973.
20. Szepietowski JC, Reich A. Pruritus in psoriasis: An update. European Journal of Pain, 2016. 20: 41–46.
21. Taneda K, Tominaga M, Negi O, Tengara S, Kamo A, Ogawa H, Takamori K. Evaluation of epidermal nerve density and opioid receptor levels in psoriatic itch. *Br J Dermatol.* 2011;165:277–284.
22. *Zhao X, Xu Y, Zhao Q, Chen CR, Liu AM, Huang ZL.* Curcumin exerts antinociceptive effects in a mouse model of neuropathic pain: descending monoamine system and opioid receptors are differentially involved. *Neuropharmacology. 2012 Feb; 62(2):843-54.*
23. Whim WS, Tak MH, Lee MH, Kim M, Kim M, Koo JY. TRPV1 mediates histamine-induced itching via the activation of phospholipase A_2 and 12-lipoxygenase. The journal of Neurosicience. 2007;27(9):2331-2337.
24. Yeon KY, Kim SA, Kim MK, Ahn DK, Kim HJ, Jung SJ. Curcumin produces an antihyperalgesic effect via antagonism of TRPV1. J Dent Res. 2010. 89(2):170-4.
25. Nast A, Jacobs A, Rosumeck S, Werner RN. Efficacy and Safety of Systemic Long-Term Treatments for Moderate-to-Severe Psoriasis: A Systematic Review and Meta-Analysis. J Invest Dermatol. 2015;135(11):2641.

Appendix A. Baseline and after four weeks of turmeric 1% cream in two patients (Patient 1: a-b & patient 2: c-d)



Acknowledgment: The authors would like to thank Dr. Mara Evangelista-Huber for her writing assistance, technical editing, and proofreading.