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CLINICAL EFFICACY OF A TOPICAL CYTOKINE INHIBITOR COMPARED TO COMMONLY PRESCRIBED DRUGS FOR THE TREATMENT OF PSORIASIS, ECZEMA AND DERMATITIS

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ABSTRACT

Psoriasis, Eczema, and Dermatitis (PED) are widespread, chronically recurrent skin conditions affecting millions of people worldwide. Their cause, while difficult to identify exactly, is often linked to autoimmune dysfunction, environmental factors, and hereditary hypersensitive terrain. Although slightly different symptomatically, all PED lesions present multiple immunologic cells at the lesion site. Excessive topical production of various cytokines, 11 of which identified as cell growth-stimulating, causes inordinate epidermal cell growth, desquamation, sloughing, and development of PED lesions. Available treatments block one or two cytokines or cellular functions, but none eliminates all the cytokines involved in PED development and persistence, while new biological drugs induce serious side effects.

Being proteins, cytokines can be blocked with specific plant procyanidins. We incorporated these tannins in an osmotically active solution to add hydrating and cleaning properties. Clinical efficacy of this topically applied solution (VB-DERM) was compared with commonly prescribed drugs (CPD).

A 6-week, controlled trial was conducted on 107 patients presenting open PED lesions. 57 patients in the VB-DERM group and 51 in the CPD group were treated to evaluate their effects on PED symptoms and quality of life.

Multiple cytokine inhibitor VB-DERM induced highly significant improvement, compared to CPD, in PED erythema, edema, oozing, pruritis, lesion healing, and patient quality of life, after only 2 weeks of application. Identical basic PED physiopathology involves excessive cell growth attributable to multiple cytokines cascade. Inhibiting these cytokines, along with cleaning and hydrating lesions through a mechanical method, represents a breakthrough approach to treat PED.

Key words: Psoriasis, Eczema, Dermatitis, cytokines, tannins

INTRODUCTION

Psoriasis, Eczema, and Dermatitis (PED) are widespread, chronically recurrent skin conditions affecting millions of people worldwide.[1] Although the exact mechanism of origin of these diseases still remains a mystery, genetic immune dysfunction leading to excessive, topical immune reaction to skin cells have been suggested as the key factor.[2,3] The fact that concordance rate is nearly 60-70% in monozygotic twins compared to only 15-20% in dizygotic twins, confirms the hypothesis of an initial immune disturbance. Although PED are classified as separate diseases based on their symptomatic appearance, the basic pathology always involve an uncontrolled and excessive keratinocyte cell growth, followed by secondary chronic pustular or non-pustular infection.[4] All PED skin lesions show the presence of multiple chronic inflammatory cells, particularly the dendritic cells,[5] T-cells, keratinocytes, natural killer (NK) cells, macrophages, and Langerhans' cells,[6] all involved in the production of various types of cytokines and growth factors.

Any cellular damage in the skin causes cell death and initiation of an inflammatory reaction. Dead cell proteins act as antigens leading to dendridic cell activation. These antigens are degraded into peptides, complexed with cellular MHC and presented to the T-lymphocytes which activate synthesis and release of cytokines, thus resulting in antigen-independent activation of T lymphocytes.[7,8] This further leads to the release of additional cytokines and the activation of a cytokine release cascade.

Cytokines are very small protein messenger molecules (a few are glycoproteins) that are secreted mainly by activated lymphocytes and macrophages, often as a reaction to an injury. More than 30 cytokines have been identified in the PED-types of lesions, including Tumour Necrosis Factor (TNF) α and γ, interleukins (ILs), interferons, chemokines, GMCSF (granulocyte macrophage colony stimulating factor), and FGF (fibroblast growth factor), most of them either acting as, or triggering synthesis of, growth factors. These growth factors continue stimulating keratinocyte production, leading to epidermal hyperplasis and the development of PED-types of lesions.[9,10]

Therefore, Shrivastava et al.[11] identified 11 cytokines which were found to stimulate epidermal cell growth synergistically. They equally suggested topical use of specific plant tannins or their fractions, such as the procyanidins (PCDs), to inactivate all PED-involved cytokines as a breakthrough and safe scientific approach to treat PED. PCDs were incorporated into an osmotically active solution[11] so as to clean the injury and normalize dermal cell growth.[12] 116 patients suffering from PED were treated either with the specific

plant PCDs incorporated into a hypertonic solution (VB-DERM) or with commonly employed PED treatments to compare their respective efficacy.

CLINICAL EVALUATION: MATERIALS & METHODS

A controlled clinical trial was conducted over a 6-week period to evaluate the safety and efficacy of VB-DERM for the treatment of all types of PED lesions and their symptoms, compared to the classical treatments commonly prescribed for those chronic conditions.

Location: This clinical study was conducted by the Bhavan Research Centre in Indore, India, between 02-2011 and 06-2012, in the dermatology department of the Geeta Bhavan Hospital and Research Centre, Indore.

Ethical Aspects: The study was performed with a EU certified medical device (CE n° 0459) and was approved by the Institutional Review Board/ Independent Ethical committee respecting GCP (Good Clinical Practice) and following the principles laid down in the declaration of Helsinki and amends thereafter. Only those subjects who gave their informed consent were included in the study. Patients not willing to try a new treatment (VB-DERM®) were given a classical PED treatment and were included in the CPD group.

Inclusion and Exclusion Criteria: The main inclusion criteria were: 1) patients having single or multiple localized skin lesions for at least the last 6 weeks, which were diagnosed either as psoriasis, eczema, or dermatitis by the dermatologist during the 1st visit; 2) male or female above 3 years of age; 3) having lesions which could be measured and covering a surface area of at least 3cm^2; and 4) ready to visit the hospital at planned intervals.

Exclusion criteria were: 1) patients having a very debilitating health condition; 2) not able to visit the hospital, or not able to read or write; 3) under treatment for other serious diseases such as cancer; 4) sensitive or allergic to herbal medicines; 5) with a history of tubercular, syphilitic, or viral skin infections; 6) diagnosed with any serious hepatic, renal or other disease based on recent (0-16 weeks old) haematological, blood biochemical or urine analyses; 7) under any systemic therapy for PED for the last 15 days.

Randomization: The selected patients were randomized and divided into two groups as follows: (1) CPD (Commonly Prescribed Drug) group patients: This group of patients included the patients who met the inclusion criteria but were reluctant to use VB-DERM. They were enrolled in the study and were prescribed any treatment which was considered appropriate by the dermatologist, according to the lesion; and (2) Active treatment VB-DERM group: all other patients who were not using any treatment or who were applying a non-medical treatment.

It was decided to stop the study or exclude the patient in case of any critical events or in case of any serious undesirable event.

Study Design: VB-DERM was applied topically (approximately 1ml / 5cm^2 surface), twice a day, for a maximum period of 6 weeks. If the lesions were not open (covered with a layer of dead keratinocytes), the lesion surface was gently scrapped with a plastic comb before product application.

CPD group patients followed treatment directions recommended by their medical advisor, but all patients were asked to fill in the observation form. The different treatments prescribed fell into 7 general categories: AH: antihistamines / anti-inflammatory drugs; C: corticosteroid topical treatments (creams, lotions); IS: immunosuppressant drugs; PL: plant-derived drugs; AB: antibiotics and IM: immunomodulators; or Tx: multiple (ex: Vit. D + retinoid etc...) treatment. All the patients were asked to stop all treatments for 3 days prior to the start of the study.

Parameters Measured: All patients' personal details and medical history were recorded in the observation file, and they were asked to come to the hospital at the time of initial selection, and then at regular 2-week intervals (14 days, + or – 2 days, between each visit). In the rare cases when a patient was not able to visit the clinic, patient sent the information to the investigator by email or post, or the questionnaire was filled during a telephone conversation with the patient. Type of lesion (P, E or D), and localization as either face (F), body (BD), hands (H), lower limbs (LL) or feet (F), were noted.

Lesions were scored on a 0 to 4 grading scale where 0 indicated no lesion, normal condition, 1 = Mild, 2 = Moderate, 3 = Severe, and 4 = Very severe condition. Similarly, the presence of erythema and pruritus, oedema, oozing from the lesion *or* lesion dryness (only one score as lesions can be either dry or humid), lesion scaling & presence of crusts, and itching and burning sensations were also recorded. Investigator's global assessment (IGA), patient global assessment (PGA), and quality of life (QL) were also evaluated using the same scale and averaged to a mean score on weeks 0, 2, 4, and 6 to determine global efficacy.

After initial screening of 128 patients, 116 patients were selected for the study and were allocated to one of the two groups. 107 final results were obtained for analysis: 56 patients in the VB-DERM and 51 in the CPD group as indicated in the COHORT flow chart (Fig.1).

Result Interpretation: For each group, the mean scores obtained at each time point for each parameter were calculated (± Standard Deviation) and compared with the corresponding values of the other group to evaluate the effects of VB-DERM compared to the CPD group.

Data Analysis: Data were analyzed using SAS 9.1.3. statistical program. Statistics, i.e. mean values, standard deviation (SD), minimum and maximum frequency distribution, were used for the analysis of demographic details, clinical evaluation, and medical history. If the p-value was greater than 0.05, the results were considered statistically not significant.

RESULTS

Subject Demographics and Distribution:

A total of **128** individuals were initially checked for recruitment. After screening according to the inclusion and exclusion criteria described above, **116** patients were selected to participate in the study.

12 patients were first excluded, either because they did not meet the inclusion criteria, or they were barred from participating due to one of the exclusion criteria. Another 9 patients dropped from the trial at some point because they left the city, or were lost to follow-up for diverse reasons.

Thus, out of the 116 patients first enrolled in the study, **107** final results were obtained.

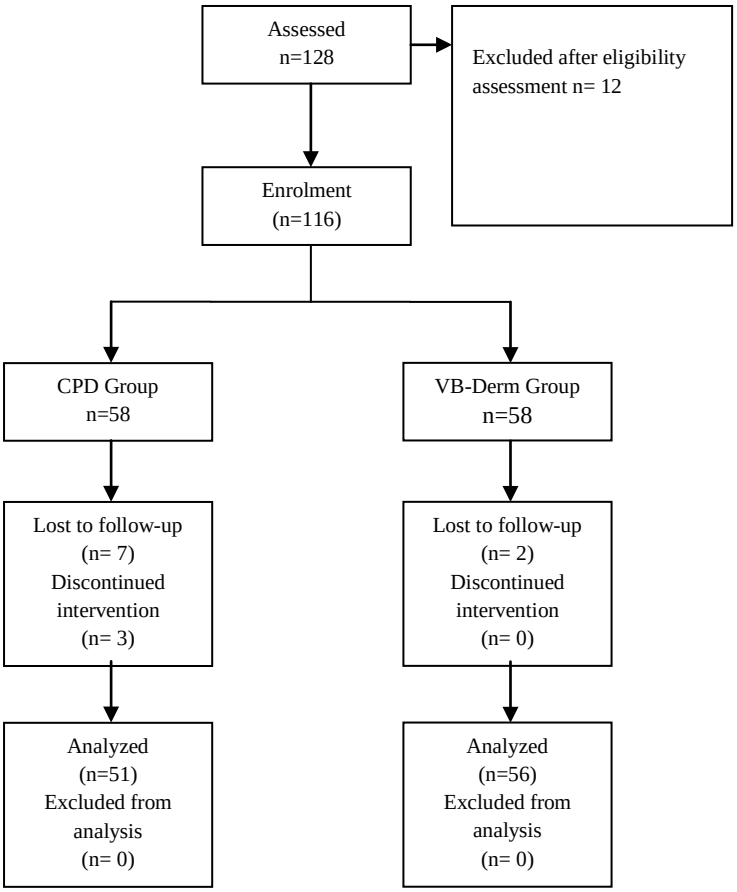

Figure 1: CONSORT Flowchart

Lesion Distribution: The distribution of a total of 107 subjects between the ages of 5 and 81 years, with mean age: 43.24 ± 9.3 years, was fairly homogenous between VB-DERM® and CPD groups with respect to age, sex, and initial oral PED symptoms. The number of patients was intentionally kept slighter higher in the VB-DERM group as the efficacy of classical treatments is fairly well known.

Among 51patients in the CPD group and 56 in the VB-DERM group, 20%, 37% and 43% subjects in the CPD group and 27%, 23% and 48% participants, had psoriasis, eczema or dermatitis, respectively.

Location of the Lesions: Both groups included patients having lesions distributed on different areas of the body with comparable numbers in each group as shown in **Table 1**.

CPD treatments: Among 51 patients in the CPD group, 7 were treated with AH, 24 with C, 7 with IS, 1 with PL, 6 with AB, 4 with IM and 2 with Tx.

PED symptom relief: The results are given in the **Table 2**.

***Table 1**: Type of lesions and part of the body affected in the patients who completed the study.*

Group	Type of lesions %			Part of the body affected				
	Psoriasis	Eczema	Dermatitis	Face	Body	Hands	Lower limbs	Feet
CPD n=51	20	37	43	15.69	23.53	7.84	23.53	29.41
VB-DERM N=56	27	23	48	14.29	16.07	16.07	30.36	23.21

***Table 2**: Percentage of reduction in mean severity scores week 2 and week 6 compared to week 0 in CPD group vs VB-DERM group*

CPD	**Erythema Pruritus**	**Edema**	**Oozing**	**Dryness**	**Scaling Crusts**	**Itching**	**Total /20**	**Investigator global assessment Score**	**Patient assessment Score**	**Quality of Life**	**Mean Score**
Mean T0	2,471	2,373	1,902	1,314	1,765	2,804	2,525	3,078	2,931	2,431	2,742
Mean T2	2,412	2,314	1,804	1,373	1,706	2,412	2,404	3,078	2,775	2,157	2,603
% Reduction T2-T0	**-0.02**	**-0.02**	**-0.05**	**+0.45**	**-0.03**	**-0.14**	**-0.05**	**0**	**-0.05**	**-013**	**-0.05**
Mean T4	2,353	2,157	1,941	1,490	1,412	2,176	2,306	2,775	2,676	2,059	2,454
Mean T6	2,235	2,098	1,961	1,353	1,451	1,902	2,200	2,696	2,480	1,902	2,320
% Reduction T6-T0	**-9.55**	**-11.59**	**+3.1**	**+2.97**	**-17.79**	**-32.17**	**-12.87**	**-12.41**	**-15.39**	**-21.76**	**-15.39**

VB-DERM	Erythema Pruritus	Edema	Oozing	Dryness	Scaling Crusts	Itching	Total /20	Investigator global assessment Score	Patient assessment Score	Quality of Life	Mean Score
Mean T0	2,643	2,393	2,036	1,161	1,161	2,732	2,425	2,848	2,580	2,661	2,629
Mean T2	1,250	1,089	1,054	0,554	0,786	1,339	1,214	1,839	1,964	2,009	1,757
% Reduction T2-T0	**-52.7**	**-54.49**	**-48.23**	**-52.28**	**-32.3**	**-50.99**	**-49.94**	**-35.43**	**-23.88**	**-24.5**	**-33.17**
Mean T4	0,857	0,911	0,804	0,321	0,482	1,089	0,893	1,214	1,429	1,411	1,237
Mean T6	0,625	0,607	0,661	0,250	0,411	0,875	0,686	0,938	1,107	1,071	0,950
% Reduction T6-T0	**-76.35**	**-74.63**	**-67.53**	**-78.47**	**-64.6**	**-67.97**	**-71.71**	**-67.06**	**-57.09**	**-59.75**	**-63.86**

Effects on Erythema and Pruritus: The severity of erythema and pruritus remained fairly stable for the control group, with only a 10% reduction in severity after 6 weeks of treatment, reported mostly by patients most affected initially. In comparison, a dramatic amelioration among patients treated with VB-DERM was quickly noticeable with a 52% reduction as early as 2 weeks into the treatment. Alleviation of this symptom was reported by the vast majority of VB-DERM patients, independently of initial severity. At the end of the study period, mean reduction was of 76% compared to pre-treatment values, with a noteworthy absence of report of high symptom severity, as the number of patients still suffering from severe and very severe erythema and pruritis had by then decreased by 84% and 100% respectively.

Effects on Edema: While among CPD patients a slight amelioration (11% reduction compared to pre-treatment) in edema severity was observed after 6 weeks of treatment, the prevalence of moderate to very severe symptom actually remained fairly stable over time, with even 3 instances of symptom worsening mid-study.

In contrast, the VB-DERM group registered a sharp decrease in the number of patients reporting severe to very severe edema as early as from week 2, with 55% mean reduction, compared to week 0. This trend remained consistent throughout the trial, with 67% reduction in severity after 6 weeks of applications, compared to pre-treatment, resulting in the number of edema-free patients quadrupling by the end of the study.

Effects on Lesion Oozing: About 60% of patients in each group showed moderate to very severe oozing, with a very similar repartition between CPD and VB-Derm groups at week 0.

Patients treated with VB-Derm presented a dramatic improvement of oozing compared to patients in the control group. Indeed, for a significant number of CPD patients (11), symptoms did not improve, but even appeared to worsen (increasing by 1 severity indicator

step) in spite of their treatment, and mean value at week 6 was actually 3% higher than at study outset, a trend contrary to the desired evolution.

In contrast, while there were 2 instances of patients reporting a slight aggravation among the VB-Derm treated population, the vast majority reported dramatic and rapid alleviation in oozing severity, diminished by 48% in the second week of treatment. The relief was most remarkable among the most severely affected patients who had all improved by week 6. At the end of the study, a global mean reduction of 67% compared to pre-treatment was observed among VB-Derm patients, with 57% of them symptom-free and none reporting very severe oozing anymore.

Effects on Lesion Dryness: Results show very clearly that the various CPD treatments proved mostly ineffectual in reducing dryness. Mean severity actually increased by 3% after 6 weeks, compared to start of the study, and 5 patients exhibited a notable worsening of the symptom, as prevalence of very severe dryness increased by 60% by week 2, to remain stable thereafter.

In contrast, as early as 2 weeks into the treatment, VB-DERM patients suffering from the most severe dryness had all improved dramatically, and the progression was regularly maintained throughout the study, with over 50% reduction in severity after 2 weeks, and 78% after 6 weeks of VB-DERM treatment, compared to baseline values.

Effect on Scaling and Crusting: At the start of the study, scaling and crusting were more prevalent in CPD patients, with 38 patients exhibiting the symptoms, for only 25 in the VB-DERM group.

These symptoms were diminished by nearly 18% after 6 weeks in the CPD group compared to 32% on week 2 already, and 64% on week 6 in the VB-DERM group.

Effect on Itching: In the CPD group, we observed a notable decrease in number of patients reporting most acute itching, and mean severity was diminished by 32% by the end of the study period. In the VB-DERM group, however, results were more significant as severity was reduced by 51% as early as on week 2, with 68% global reduction recorded on week 6, compared to week 0.

Visible Lesions: In the CPD group, the mean score was diminished by nearly 5% only versus 50% for VB-DERM on week 2 and by 13% versus over 70% for VB-DERM by week 6. While complete lesion healing was not always attained for all VB-DERM patients even after 6 weeks of treatment, the results obtained with VB-DERM are highly significant statistically. VB-DERM acts on the symptoms of PED with remarkable efficacy.

Global Assessment and Quality of Life: The global severity of the disease assessed by the investigator and by the patients were fairly identical. The average improvement in their global assessment, after 6 weeks of treatment, was nearly 14% in the CPD group. In accordance with the significant symptomatic relief observed across all parameters in the VB-DERM group, their average global assessment had improved by 29% after 2 weeks and 62% after 6 weeks. Closely reflecting those results, the improvement in quality of life, after 6 weeks of treatment, was nearly 15% in the CPD group but reached 63% in the VB-DERM group.

Global Mean Score: In the CPD group, global symptom amelioration was quite progressive over time, and rather comparable in all age groups, but varied somewhat according to the lesion's location on the body. Reversely, VB-DERM patients' response to treatment was much more rapid and significant. The location of the lesions, initial severity of the disease or the age of the patient had no effect on treatment outcome **(Fig. 2).** VB-DERM was found equally effective for the treatment of psoriasis, eczema and dermatitis, as shown in the **Fig. 3**. No side effects or undesirable reactions were noted in any of the patients except for initial and transient local irritation in about 15-20% of patients during the first half hour, in both groups.

These results indicate that a topical multiple cytokine inhibitor associated with a hypertonic solution represents a very effective and safe remedy to treat PED-types of lesions.

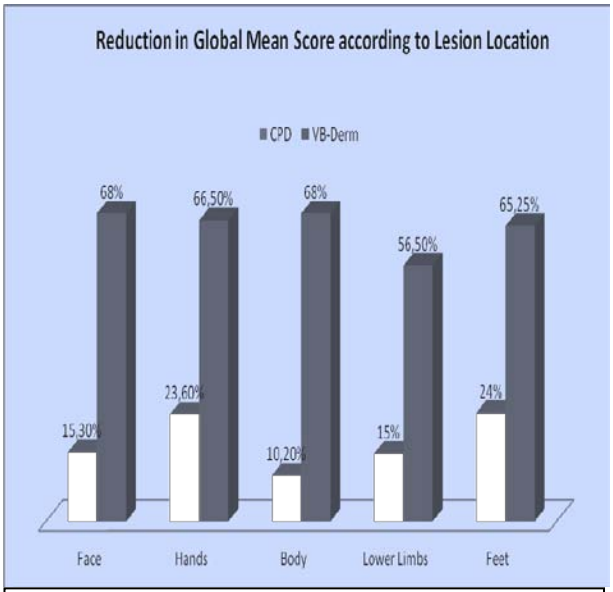

Figure 2 – Comparison VB-DERM vs CPD group with respect to location of the lesions on the body.

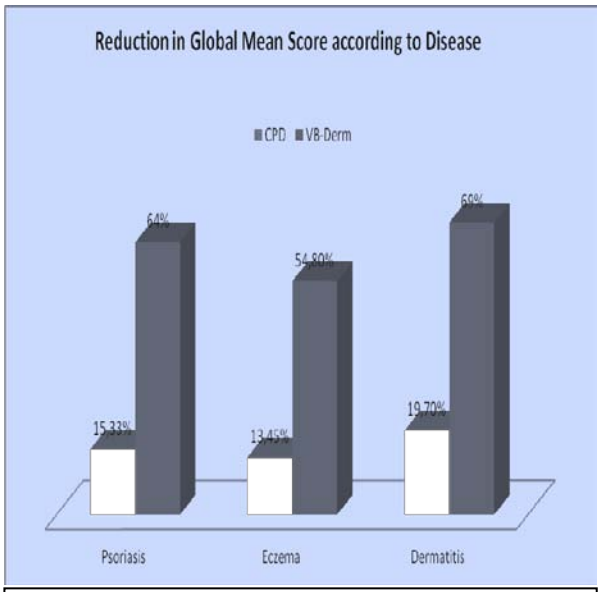

Figure 3 – Comparison VB-DERM vs CPD group on the lesions diagnosed as psoriasis, eczema or dermatitis.

Results are expressed as % improvement compared to baseline values. ($p<0.05$ at all time points compared to the CPD group).

DISCUSSION

Psoriasis, Eczema & Dermatitis are considered as cell-mediated hypersensitivity reactions, but the exact etiology is unknown.[13] The pathogenesis is multifactorial and involves a complex immunologic cascade in the dermis and epidermis, including disruption of the epidermal barrier, defects in the cutaneous cell-mediated immune response, flooding of the lesion with multiple growth factors like cytokines, resulting in skin hyperplasia and dermal sloughing. The immune cells found in majority in the lesion are Langerhans' cells, inflammatory dendritic epidermal cells, monocytes, macrophages, natural killer (NK) cells, lymphocytes, mast cells, and keratinocytes,[14] all of which interact through an intricate cascade of cytokines, particularly the ILs, TNF- α, and growth factors.

Worldwide, considerable scientific efforts have been undertaken to characterize the causes of PED, but unlike other common tissue-specific autoimmune diseases, PED does not have a generally accepted animal model, and our understanding of its pathogenesis is primarily obtained from clinical studies and translational science on affected patients. This research initially focused on T lymphocytes as principal inducers of cellular changes,[15] followed by the role of interleukines,[13,16] TNF- α[17] and other cytokines,[18,19] but now it is fairly well accepted that some genetic factors modulating skin sensitivity to antigens play a significant role in triggering the disease. As it is presently extremely difficult to modify the body's immune mechanism, the treatment of PED remained symptomatic (antiseptics, antibiotics, anti-inflammatory drugs) or directed at a particular immune function. Initially, the commonly employed anti-cancer drug methotrexate, or immunosupressants such as cyclosporine were used to suppress the disease but the multiple side effects of these drugs limited their use. When the T-cell hypothesis was confirmed,[20] inhibitors of T-cell activation such as alefacept were employed with limited success. When the mechanism underlying psoriatic inflammation was accepted as a cytokine network disorder, more specific biologics were studied in murine models and were later used clinically.[21,22] Tumor necrosis factor was the first direct cytokine inhibition therapy marketed under different names such as infliximab, adalimumab, and etanercept.[23] With the recently discovered role for Th-17 in autoimmunity, drugs targeting interleukin-23 (ustekinumab) are now being proposed as new therapies.[24] New biological drugs such as alefacept, a fusion protein that binds to CD2 on T cells, and efalizumab, a humanized antibody that binds to leucocyte function associated antigen-1 (LFA-1), an integrin expressed at high levels on T cells are also introduced on the market.[25]

Unfortunately, none of these treatments may be considered sufficiently efficient, while they have multiple side effects due to their systemic administration affecting the whole body's immune functioning.[26] This is imputable to the fact that PED-type diseases are not caused by a single cell type or a single inflammatory cytokine, but result from the over-expression of a few cell growth-stimulating cytokines,[27] produced in abundance at the epidermis and dermis levels.[4] Therefore, a promising treatment lies not in inhibiting the activity of a particular cell type or cytokine, but in identifying and blocking comprehensively and exclusively those cytokines which trigger uncontrolled cell growth. Such a treatment should act only topically on the surface of the lesion to avoid influencing the normal immunological functions of the body. It should equally eliminate all contaminants from the lesion to reduce itching and irritation while keeping the lesion humid, and must be non-toxic to the cells.

In a previous study, 11 cytokines were identified (Shrivastava et al. 2013) acting in synergy to initiate and maintain excessive epidermal cell growth. These cytokines are proteins and act as cell growth factors. Inhibiting the activity of one or two of these cytokines would reduce the cell growth to some extent but other cytokines would still continue stimulating cell growth, thereby minimizing the effect of any partially cytokine-blocking drug. Inhibiting all these cytokines at once was never envisaged because the specific cytokines involved in cell growth were never identified, and there is no chemical, biological, pharmacological or immunological mechanism capable of selectively destroying only those cell growth-enhancing cytokines, the basic cause behind PED.

Tannins are very big molecules with multiple OH groups having a strong capacity to bind with proteins. Tannins are semi-specific with respect to their protein binding properties as they can link not with all but at least 4-5 proteins at a time. An association of three different plant tannins, called VB-PCDs was incorporated in a hypertonic osmotically active filmogenic solution (VB-Gly) so as to form a film over the lesion surface. Tannins bind to the selected cytokines while osmotic activity of VB-Gly attracts hypotonic liquid from the inner parts of the lesion, cleaning the lesion of bound tannin–cytokine complexes as well as of all other contaminants present on the lesion's surface.[28] Absence of contaminants and cell growth-stimulating cytokines helps normalize cell growth and the symptomatic manifestations of PED.

Tannins, being inert molecules, remain on the surface of the lesion without any chemical, pharmacological, immunological or metabolic interactions with the underlying cellular structures, avoiding all systemic biological interferences and side effects.

Results of this study demonstrate that although the lesions caused by the skin cell growth-stimulating cytokines are classified as psoriasis, eczema, or dermatitis, and further sub-divided into different categories based on the physical appearance of the lesion, the physio-pathology remains identical. In the absence of any therapy to modulate the immunological functioning of the body selectively, the use of a mechanically acting, specific cytokine inhibitor with concurrent antiseptic and hydrating properties constitutes a highly promising treatment for PED.

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The author has full control of all primary data, and was involved in the conception and design of the research, and in the acquisition, analysis and interpretation of data, and has given final approval of the manuscript to be published.

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