

Original Research Article

Glucocorticoid receptor blockage and thymidine phosphorylase inhibition: a new treatment option for psoriasis

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ABSTRACT

Background: The present study describes the efficacy of an ointment widely used in the treatment of psoriasis blocking glucocorticoid (GR) receptor in KU812 cells.

Methods: The ointment is composed of various phyto-actives source from the botanicals such as *Wrightia tinctoria*, *Cynodon dactylon*, *Boswellia serrata*, and *Hydnocarpus laurifolia*.

Results: The present findings clearly demonstrate the ointment having steroid-like effect essential for the treatment of psoriasis. The steroid like effect would hinder/reduce the inflammatory events, the major clinical manifestation in psoriasis. Further the ointment also has exhibited effect in inhibiting thymidine phosphorylase (TP) activity and thereby prevent/reduce the events that lead to angiogenesis and flow pro-inflammatory mediators at the site of lesion. Angiogenesis is one of the early changes that prelude inflammatory cascade.

Conclusions: The dual efficacy of the ointment viz., blocking GR and inhibiting TP enzyme and thereby suppressing angiogenesis clearly indicate the essential therapeutic effect of the ointment for the treatment of psoriasis.

Keywords: Psorolin B, Boswellic acid, GR receptor, KU812, Thymidine phosphorylase

INTRODUCTION

Psoriasis is an incurable, autoimmune disease of the skin, that occur as a result of the involvement complex autoimmune mechanisms where the immune system, autoantigens and variety of environmental factors contribute collectively to the above.¹ Proliferation of keratinocytes is being accompanied by dermal vascularity and immune cell infiltration and all the above three independent events have been often noticed in psoriasis.²

Boswellic acid is known to have steroid-like effect and is been used for the treatment of psoriasis.³ We, in the present study, have evaluated an herbal ointment (Psorolin B) for its steroid like activity using basophil model. Basophil contain large amount of GR site where

steroids often bind.⁴ The test formulation if has steroid like activity would bind to GR receptor in basophil and thus the treated basophil is when challenged, would not release histamine.

Further we have also studied the effect of the ointment in inhibiting TP enzyme which is responsible for vascular modification-angiogenesis which plays an important role in the clinical phase of the disease.⁵

The process of angiogenesis initiate with sprouting of new blood vessels forming a network resulting in enlarged, highly permeable cutaneous blood vessels at the site of lesion which pave the way for other series of pathological events to take place. It has been reported that the resolution of angiogenesis has always resulted in the resolution of clinical symptoms of psoriasis as well.⁶

The process of angiogenesis is being prelude by the over expression of TP enzyme. The formation of blood vessels and increased vascularity are aided by the enzyme TP and further, an increased TP activity and increased keratinocyte proliferation activity both at cell culture and *in vivo* methods have been noticed which clearly indicate the role of this enzyme in providing thymidine/thymine is necessary for keratinocyte multiplication besides increased dermal vascularity due to angiogenesis which further facilitate immune cell infiltration and accumulation at the site.⁷

Silencing, at least partly, the enzyme TP may offer the much-needed relief as the accumulation of this enzyme at the site of psoriatic lesion and its definite role in the pathology of the disease are well established.⁸ Mutilation of this enzyme may offer limiting the vascular bed formation and inflammatory events to take place.

In the present study we report the effect of the herbal ointment in blocking GR receptor and inhibiting TP enzyme suggesting the possible treatment benefit for psoriasis. Details are presented in the article.

METHODS

Details of the herbal ointment

The study is an *in vitro* enzymatic investigation. The ointment is made with the base material such as stearic acid, cetostearyl alcohol, and liquid paraffin, petrolatum besides vitamin D, vitamin E, and wheatgerm oil. The ointment also has extracts of following medicinal herbs such as *Wrightia tinctoria*, *Boswellia serrata*, *Cyanodon dactylon*, *Hydnocarpus laurifolia* and the mineral-red ochre.

GR receptor blockage

For the present study, KU812 cell line was used in lieu of basophil. In brief, the basophil-like cell line (KU812) was grown in RPMI 1640 with fetal bovine serum (FBS), penicillin-streptomycin in cell culture plate.

Anti-IgE or the specific allergens were used for the stimulation of the cells. Histamine thus released was quantified by ELISA.

The frozen basophil-like cells (KU812) and was brought to 37°C using water bath. Then the cells were transferred to 15 ml conical tube containing 10 ml of pre-warmed RPMI-1640 medium supplemented with 10% FBS and 1% penicillin-streptomycin.⁹

It was centrifuged at 300 g for 5 minutes and then discarded the supernatant and re-suspended the pellet in 10 ml of fresh RPMI-1640 medium with 10% FBS and 1% penicillin-streptomycin. Then transferred the cells to culture flask and incubated at 37°C in a humidified incubator with 5% CO₂.

The cultured cells after reaching the density of 0.5-1×10⁶ cells/ml were diluted to 1:2 to 1:4 with fresh medium.

Stimulation and histamine release assay

The harvested the cells after centrifugation at 300 g for 5 minutes were re-suspended in fresh RPMI-1640 medium and the cells were adjusted to a concentration of 1-2×10⁶ cells/ml. Then the cells were plated in a 96-well plate at 100 µL per well. Then added anti-IgE or substance P to stimulate the histamine release. Similarly, maintained a control wells with no stimulation (negative control) and as well as with a known histamine releaser (positive control, ionomycin and PMA-Phorbol myristate acetate).¹⁰ The cell culture plate was incubated at 37°C in a humidified incubator with 5% CO₂ for 30 minutes to 2 hours, depending on the kinetics of histamine release. After incubation, the cells were centrifuged at 300 g for 5 minutes to pellet the cells. Carefully collected the supernatants from each well and then transferred them to new tubes or wells for histamine measurement.

Before stimulation, the cells were treated with by the test material at varying concentrations such as 10, 20, 30, 40, 50 micrograms per millilitre.

In vitro TP assay

The TP enzyme inhibition assay was performed in 96 well plate; where the experiment was repeated thrice to validate the result. In brief, 200 micro litre of reaction mixture made with 10 micro litre of the test compound (s) (0.5 mM; in DMSO) 150 micro litre of potassium phosphate buffer (pH7.0, 50 mM), and 20 micro litre of TP enzyme (0.058 unit/well). The plate with all reagents was incubated for 10 minutes at 30°C. After incubation, 20 micro litre of 1.5 mM substrate-thymidine was added and changes in O.D. was read at 290 nm for 10 minutes using spectrophotometer.¹¹

The IC₅₀ represents concentration of compounds that inhibit the degradation of thymidine to thymine by 50%. It was calculated by measuring the effects of different concentrations of inhibitors on the degradation of thymidine. The percentage inhibition was calculated by using the formula-

$$\% \text{ inhibition} = 100 - \frac{\text{Absorbance of test compound}}{\text{Absorbance of control}} \times 100$$

RESULTS

The herbal ointment despite the concentration tested has shown GR receptor binding and hence the subsequent stimulation did not release histamine and released histamine level was far too insignificant when compared to control.

Among the four herbs tested for TP inhibition activity, *Hydnocarpus laurifolia* exhibited highest activity over

other herbs. *Wrightia tinctoria* was next in the order and a marginal correlation in the activity versus concentration of all herbs was observed. The ointment however showed highest TP inhibition and we could not find great linearity between concentration and efficacy.

Table 1: GR receptor binding lead decrease in histamine release by KU812.

Test detail	Concentration (µg/ml)	% of histamine released from basophil
Herbal ointment	10	2
	20	4
	30	4
	40	5
	50	5
Control		65

Table 2: TP inhibition assay.

Test details	% inhibition of TP and concentration in microgram per millilitre		
	10	20	30
<i>Wrightia tinctoria</i>	33	41	48
<i>Boswellia serrata</i>	22	25	28
<i>Cyanodon dactylon</i>	11	19	21
<i>Hydnocarpus laurifolia</i>	43	49	53
Herbal ointment	51	59	68

DISCUSSION

Treatment of psoriasis requires a new strategy and approach because of the underlying inflammatory predisposition and incurable nature of the disease. Herbal preparations have shown limited level of therapeutic value in bringing down some of the key symptoms of psoriasis such as scaling or itching and the early inflammatory changes. However relatable mechanism of action and rigorous scientific validation were lacking for most herbal preparations and hence the therapeutic value was always doubted.

The herbal ointment (Psorolin B) has shown remarkable therapeutic effect in the treatment of psoriasis where the inflammatory manifestation, itching and scaling have shown significant reduction after using the ointment for three months in psoriatic patients.¹²

In order to understand the possible mechanism of action of the ointment we studied the GR receptor blockage and TP inhibition at *in vitro* level. Boswellic acid is richly present in the plant *Boswellia serrata* and is vastly used

in treating inflammatory diseases such as arthritis, chronic joint pain etc.¹³

In our present study we found that the basophil like cell line (KU812) were treated with the herbal preparations showed low level of histamine release in response to the trigger by PMA. The cell line has significant glucocorticoid/ steroid receptor for the steroid to bind and thus suppress the cells. The ointment treated basophil showed reduced level of histamine release despite the trigger by PMA which strongly support the possible GR receptor blockage. The findings thus suggest steroid like effect of the ointment which is necessary for treating psoriasis. The advantage of the ointment over steroidal preparation is the steroid like activity where the treatment outcome is favourable but the side effects are least to the nil.

The angiogenetic change in psoriasis also was found to decrease after treatment with the ointment. Therefore, we speculated that the ointment may have effect in inhibiting TP enzyme which is responsible for the angiogenetic cascade. TP enzyme accumulation is reported in psoriatic lesion which is responsible for the conversion of thymidine to thymine which accelerate both cell division and increased vascularization in other words, angiogenesis.^{5,7}

In the case of psoriasis, the increased angiogenesis not only results in increased nutrient transport to increase the cell division but also the transportation of several pro-inflammatory mediators to elicit strong inflammatory response especially at the site of lesion. Psoriasis requires both suppression of cell division and decreasing angiogenesis in order to prevent the inflammatory elicitation. Once such treatment strategy is achieved, the clinical manifestation of the disease can be kept calm and manageable. The question of when the inflammatory trigger would cascade the entire pathological events in each patient is not known but certainly every psoriatic patient would undergo such inflammatory phase and therefore continuous use of ointment from the day of diagnosis of the disease may necessarily help them to manage the disease well.

The ointment has already been tested for its effect in inhibiting collagenase, elastase, free radical generation, cellular glycation process and histidine decarboxylase besides keratinocyte proliferation and differentiation and S100A7 protein expression.¹⁴⁻¹⁶ The present investigation has brought out an additional therapeutic benefit that is steroid-like effect and TP enzyme inhibition resulting in the suppression of angiogenesis and most of the psoriasis symptoms.

Several factors are responsible for triggering the inflammatory process and often steroidal preparation is used to manage the problem. Considering the broad pharmacological benefit of the ointment, best treatment benefit can be achieved along with least side-effects.

CONCLUSION

The present study clearly confirms the usefulness of the ointment in the treatment of psoriasis by having both steroid-like effect and inhibiting angiogenesis through TP inactivation. For the management of psoriasis, the ointment may be used as the active ingredients are essentially sourced from botanicals and are safe for long term usage.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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