

## CONVENTIONAL TOPICAL TREATMENTS OF PSORIASIS

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### Summary

The scenario of this study was to review and explore the currently used topical allopathic remedies in the treatment of psoriasis. Psoriasis is a non-infectious, recurrent and inflammatory disease of the skin, characterized by erythematous plaques with large silvery scales due to excessive maturation of keratinocyte cells. The exact causes of psoriasis are unknown but assumed to be an autoimmune inflammatory disease with a genetic basis. Various topical agents such as tar, dithranol, corticosteroids, salicylic acid, methotrexate, allantoin has been used for treating psoriasis and several reports claim to treat the psoriasis.

**Keywords:** Psoriasis, Methotrexate, Corticosteroid, Allantoin, Tar

### Introduction

Psoriasis is a chronic, recurrent, inflammatory skin disease that affects 2% to 3% of the population worldwide and causes significant morbidity<sup>1</sup>. Classic lesion is a well-marginated, redness of the skin due to pathological changes, erythematous plaque with silvery-white surface scale, mainly distributed into extensor surfaces (i.e., knees, elbows, and buttocks); may also involve palms and scalp. Associated findings include psoriatic arthritic and nail changes<sup>2</sup>. These are inflammation, hyperproliferation of the epidermis, vascular alterations which add to the redness<sup>3</sup>. Its exact etiology is unknown, but it is generally believed to be a complex autoimmune inflammatory disease with a genetic basis<sup>4</sup>. Histologically, psoriasis is characterized by acanthosis (thickened epidermis) and parakeratosis (nucleated cells in stratum corneum) and has been described as showing benign hyperplasia. The dermal blood vessels are abnormally tortuous and dilated, and lymphocytic infiltration is frequently seen in the dermis and occasionally in the epidermis<sup>5</sup>. Therefore, some effective therapies appear to act as antiproliferative agents and diminished rates of either epidermal DNA synthesis, mitosis or both. Treatment of psoriasis includes topical, systemic, phototherapy and biological<sup>6</sup>, thereby; but these therapies have many side-effects.

### **Types of Psoriasis<sup>7</sup>**

There are different types of psoriasis. The most common form of psoriasis is plaque psoriasis, which accounts for approximately 85-90 percent of cases.

#### **Plaque psoriasis**

Plaque psoriasis presents as well defined, thickened, red plaques covered with silvery scales. It mainly distributed on scalp and extensor surfaces of the extremities. It is characterized by dry, scaling patches on the affected area.

#### **Guttate psoriasis**

Guttate (drop like) psoriasis is an acute form of psoriasis that usually affects children and young adults. It mainly distributed on the trunk and proximal extremities. It presents as small, scaling papules or small plaques, usually 0.5 to 1.5 cm in diameter, commonly follows a streptococcal throat infection.

#### **Erythrodermic psoriasis**

In this type of psoriasis, the skin becomes red and inflamed accompanied by severe itching and pain distributed on face, trunk, and extremities with fine scales. It can be precipitated by the withdrawal of systemic or potent topical steroids.

#### **Pustular psoriasis**

It is less common type of psoriasis, divided into two types- Generalized pustular psoriasis and Localized pustular psoriasis. Generalized pustular psoriasis is a rare form of the disease in which clusters of pustules develop on already inflamed skin of the trunk and extremities, often with sparing of the face and associated with fever, may occur in pregnancy. Localized pustular psoriasis is characterized by yellowish brown pustules on the palms or soles of the feet and nails.

#### **Nail psoriasis**

Nail psoriasis is characterized by pitting, subungual hyperkeratosis, onycholysis, yellow/brown spots under nail plate. Fingernails and toenails are affected in about 50 per cent cases of psoriasis.

### **Causes of Psoriasis<sup>8</sup>**

The numbers of factors are responsible to trigger the psoriasis such as Physical factors, Infections and Medications. The major causes of Psoriasis are mentioned in Table 1.

**Table 1: Causes of Psoriasis**

<b>Physical factors</b>	<b>Infections</b>	<b>Medications</b>
Trauma Abrasions Contusions Lacerations Burns Sunburn Bites	Viral bronchitis Streptococcal pharyngitis Human immunodeficiency virus (HIV) infection	Antimalarial agents Lithium β-Adrenergic blocking agents Corticosteroid withdrawal

### Histopathology of Psoriasis

#### Epidermal Hypothesis

There is a great acceleration of the transit time of cells from the basal cell layer to the uppermost row of the squamous cell layer from approximately 13 days in normal epidermis of active psoriatic lesions<sup>9</sup>.

Stratum corneum in psoriatic skin has holes/pores through which Stratum Corneum antigen (SCag) leaks. Stratum corneum antibody (SCab) binds to antigen forming SCag/Scab complexes that in turn bind to complement. This triggers polymorphonuclear leucocyte infiltration from the dermis into the epidermis which in turn stimulates epidermopoiesis<sup>10</sup>.

#### Dermal Hypothesis

Early capillary changes leading to disturbance in epidermal-dermal permeability<sup>11</sup>. The ultrastructure of the capillary loops in the dermal papillae shows them to be different from normal capillary loops. Normal capillary loops have the appearance of arterial capillaries. In psoriasis, however, the capillary loops have the appearance of venous capillaries<sup>12</sup>.

#### Genetic Hypothesis

A Strong association exists between the psoriatic phenotype and the HLA-Cw6 locus. The prevalence of the gene in patients with psoriasis is approximately 70%, compared with a prevalence of 10% in the normal population<sup>13</sup>. Other HLA systems associated with psoriasis are class I antigen B13, B17, B37 and class II antigen D27<sup>14</sup>.

#### Immune System and Psoriasis<sup>15</sup>

Psoriasis is the most prevalent T-cell mediated inflammatory skin disease. The three major theories of pathogenesis are as below:

- 1) Epidermal keratinocytes-derived cytokines trigger T-lymphocyte activation epidermal keratinocytes.
- 2) Antigen dependent T-cell activation generates immunologic cytokines in turn activating epidermal keratinocytes.
- 3) A third theory suggests that CD8+ 'killer' T-lymphocyte is autoreactive with epidermal keratinocytes and trigger epidermal activation by autoimmune reactions.

The following steps will help us to understand activation of immunological system better.

#### Step 1

APC (Antigen Presenting Cell) in the epidermis & dermis called as LC (Langerhans cells) in epidermis and DDC (Dermal Dendritic cells) in dermis

↓  
Capture antigen, process and express it on cell surface for naïve T-cells

↓  
LC and DDC required for T-cell activation

#### Step 2

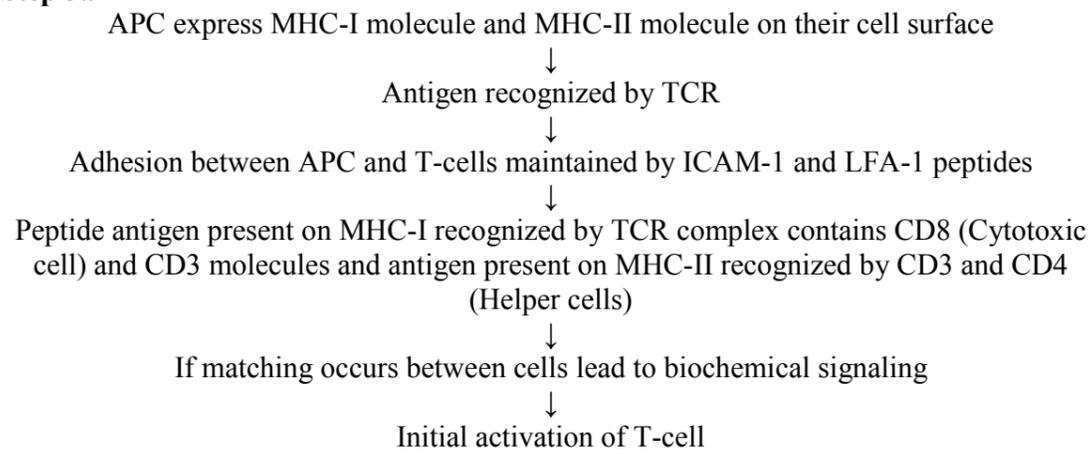
Activated DDC migrate to lymph node

↓  
Bind with it and activate T-cells.

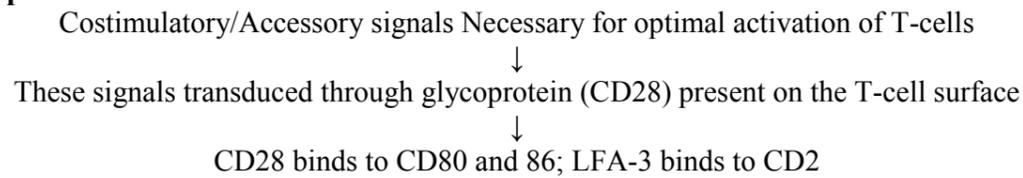
↓  
Generalisation of T-cell, B-cell and Memory T-cell, B-cell

#### Step 3

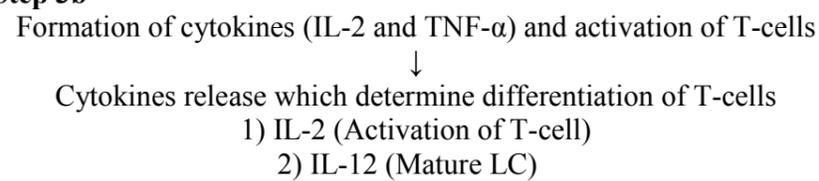
**Step 3a**



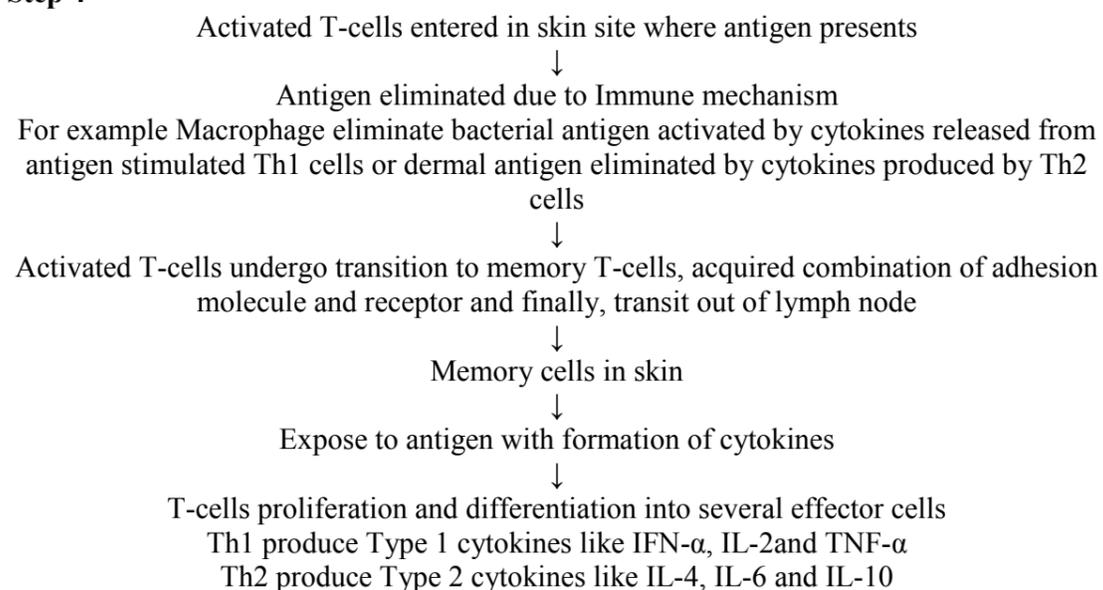
**Step 3b**



**Step 3a + Step 3b**



**Step 4**



So, infiltration of inflammatory cells and epidermal proliferation with abnormal keratinocyte differentiation to be driven by various cytokines released.

### **Topical treatment of Psoriasis**

Emollients and baths are helpful in restoration of the stratum corneum barrier function and are characterized by an increased transepidermal water loss. At the beginning keratolytic agents should be administered for shedding the scales and for a better penetration of antipsoriatics are given<sup>16</sup>. Other topical agents are Retinoids<sup>17</sup>, Vitamin D analogue<sup>18</sup>, Corticosteroids<sup>19</sup>. There is no. of topical agents used in the treatment of psoriasis which are listed in Table 2.

#### **Tar**

There are numbers of topical agents available for skin disease among them Tar is one of the good for many dermatoses for more than a 100 years. It is primarily useful before the no. of steroidal preparations used for skin disease. Tar has antipsoriatic, antiseborrheic, antipruritic and keratolytic effects<sup>20</sup>. There are different types of tar viz. shale tar, wood tar and coal tar. Among these Coal tar is very important one in the treatment of psoriasis and is a complex mixture of thousands of substances<sup>21</sup>. It can be compounded in an ointment, soap, shampoo, cream or solution vehicle in concentrations from 0.5% to 20%<sup>21,59</sup>. The clinical efficacy of crude coal tar is improved by using non-ionic surfactant. Its main effect is to suppress the DNA<sup>22</sup> as well as having antimetabolic action and is reduced the thickness of epidermis in healthy volunteers with long period treatment. Tar is used in its pure form or in combination form (salicylic acid, anthralin, calcipotriol<sup>23</sup>, corticosteroid<sup>21</sup> and UVB light- Goekerman therapy<sup>24</sup>). It is mainly applied on the scalp (shampoo, alcoholic solution), palmoplantar location (tar bath, ointment, alcoholic extract), trunk and limb (ointment)<sup>59</sup>.

Adverse effects includes Folliculitis, Tar acne, Reversible pigmentation, photosensitivity, Exacerbation of lesion, Carcinogenicity and irritation<sup>21,59</sup>. It should not be used on acutely inflamed skin, or different types of psoriasis like on pustular psoriasis or erythrodermic psoriasis<sup>25</sup>.

#### **Dithranol**

It is a Chrysorabin<sup>26</sup>, 3-methyl dithranol, obtained from *Vouacopoua araroba*, imported by Portuguese from Brazil to India<sup>27</sup>. Anthralin (dithranol) is a potent anti-inflammatory and anti-proliferative agent<sup>28,29</sup>. It is oxidized to form highly reactive free radical compounds that are thought to be inhibit DNA synthesis in psoriasis<sup>30</sup>. Some other proposed mechanisms like mitotic rate and its repair, interference with cyclic nucleotides, interference with mitochondria, interference with dendritic cells/ Langerhans cells and various interleukins such as IL-6, IL-10, IL-8 receptors. Chrysophanic acid and Chrysazin are responsible for yellow colour<sup>31</sup>. Anthralin is more commonly used in conjunction with ultraviolet B phototherapy<sup>32</sup>. Ingram therapy is also useful but it has disadvantage like cause irritation and requires hospitalization<sup>27</sup>. It is also used along with Vitamin D derivatives<sup>33</sup>. Potent corticosteroid was used along with lesional short contact dithranol therapy<sup>34</sup>. Now a days novel preparations and combinations are used viz. liposomal delivery of dithranol<sup>35</sup>, Micanol (dithranol is microencapsulated in crystalline monoglyceride)<sup>36,37</sup>. Dithranol mainly applied on scalp, external auditory meatus, face and flexures in the form of cream.

Anthralin's adverse effects include staining of skin, clothing, and furniture and may cause irritation. To reduce these adverse effect, recently a short-contact regimen (5 to 30 minutes)<sup>38</sup>, use of triethanolamine to prevent staining<sup>39</sup> and heat-sensitive preparations<sup>40</sup>.

**Table No: 2 Topical therapies for Psoriasis**<sup>44, 59-65, 67-68</sup>

<b>Topical agents</b>	<b>Mode of action</b>	<b>formulation</b>	<b>Patient acceptance</b>	<b>Efficacy</b>	<b>Duration of remission</b>	<b>Adverse effects</b>
Tar	Reduction in the thickness of epidermis	Crude coal tar, ointment, soap, shampoos, cream	Poor	Thinning of plaques, decreased symptoms in 2-4 weeks	Prolonged when combined with UV-B light, improved by using non-ionic surfactant	Irritation, photosensitivity, folliculitis
Dithranol	Interference with dendritic dermis cells and interleukins suppress hairless mouse epidermal DNA synthesis	Cream, commercial formulation	Poor	Thinning of plaques, decreased symptoms in 2-4 weeks	Prolonged when combined with UV-B light,	staining of skin, clothing, and furniture and may cause irritation
Glucocorticoid	Anti-inflammatory, immunosuppressive, antiproliferative and vasoconstrictive action	powders, solutions, sprays, creams, emollient creams, lotions, foam, gels and tape	Excellent	Thinning of plaques, decreased symptoms in first 2 weeks	Mean duration of 2 months with betamethasone dipropionate ointment	Atrophy, hypopigmentation, telangiectasias, folliculitis, hirsutism
Retinoids	To regulate keratinocyte differentiation, reverses keratinocyte hyperproliferation	Tazarotene 0.05%, 0.1% gel or cream	Good	Improvement noted in first 2 weeks of therapy	Prolonged compared to fluocinonide	Irritation; must be used with extreme caution in women of childbearing age
Vitamin D analogue	To regulate cell growth, differentiation and immune functions via acting on Vitamin D receptors	Calcipotriene cream, ointment and scalp solution	Good	Improvement noted in 6-8 weeks	Long term therapy necessary	Irritation, risk of hypercalciuria and hypercalcemia with >100g in a week
Salicylic acid	To decrease corneocyte adhesion in epidermis	OTC Solution, shampoo	Excellent	Used in combination with corticosteroid	Not applicable	Risk of salicylate toxicity with application to body surface area

**Corticosteroids**

Topical corticosteroids are most commonly and widely prescribed for different types of psoriasis like Plaque psoriasis, scalp psoriasis in all age groups. Steroids are delivered into the skin which is convenient, safe and efficacious, requires suitable vehicle i.e. well-suited to the different sites on which psoriasis occurs. No. of vehicles are available viz. powders, solutions, sprays, creams, emollient creams, lotions, foam, gels and tape<sup>41</sup>. Propylene glycol used for dissolving glucocorticoid in the vehicle leads to increase the potency of it<sup>42</sup>. Topical Corticosteroid mainly bind with high affinity to glucocorticoid receptor, which upon activation, separates from associated non-DNA binding proteins and activated glucocorticoid receptors dimerize and transport across the nuclear membrane. This dimer activates specific nuclear transcription elements and finally produces biological response. So, corticosteroids directly act on dendritic cell differentiation, cytokine inhibition, elastase expression, lymphocyte apoptosis and toll-like receptor regulation<sup>43</sup>. It has anti-inflammatory, immunosuppressive and antiproliferative action<sup>44</sup>. Corticosteroids are classified according to their potency as described in Table 3<sup>45</sup>.

**Table 3: Different types of Corticosteroids**

S. No.	Potency	Generic Name
1	Super high potency	Betamethasone dipropionate 0.05% Diflorasone diacetate 0.05% Clobetasol dipropionate 0.05%
2	High potency	Desoximetasone 0.25% Fluocinonide 0.05% Amcinonide 0.05-0.1% Halcinonide 0.05%
3	Mild potency	Mometasone furoate 0.1% Triamcinolone acetonide 0.1% Flurandrenolide 0.05% Betamethasone valerate 0.1% Hydrocortisone valerate 0.2%
4	Low potency	Hydrocortisone 0.5-2.5% Desonide 0.05% Dexamethasone 0.1%

Topical corticosteroids may be used for minimum duration. If it is used for long time, cause local as well as systemic side effects. Super high potent or highly potent topical corticosteroids used for short duration. It is usually applied to the skin b.i.d.. It mainly reduces redness and stops the rapid build-up of dead skin cells<sup>46</sup>. Corticosteroids cause various adverse effects like atrophy, striae (particularly in intertriginous areas), telangiectasia, rosacea, perioral dermatitis, glaucoma, cataracts, contact sensitization (to the steroid itself as well as to the base and preservatives), tachyphylaxis (lack of effect with continued use), flare upon discontinuation, adrenal suppression (don't use >50 mg of ultra high potency steroids/wk)<sup>47</sup>, cushing's syndrome (long term topical steroid therapy)<sup>48</sup> etc.

### **Salicylic acid**

Salicylic acid comes under the keratolytic group. It is used topically in the treatment of psoriasis. It can be useful for treating scaly, rough plaques<sup>49</sup>. It reduced the corneocyte adhesion<sup>50</sup> resulting in enhanced flaking of corneocytes<sup>51</sup>. It is found in several over the counter medicated scalp solutions, shampoos, ointments. In psoriasis, it is used in combination with corticosteroids to increase their penetration power as well as efficacy<sup>52</sup>, anthralin or coal tar<sup>53</sup>. If salicylic acid 6% gel used along with 0.1% Tacrolimus ointment shown good improvement in 46% of the patients as compare to 17% patient undergoing salicylic acid as monotherapy<sup>54</sup>.

Systemic toxicity of salicylic acid formed some adverse effects viz. dizziness, nausea, vomiting, stupor, confusion, coma, death and hypoglycemia in patients suffering from anaemia<sup>51</sup>.

### **Methotrexate**

Methotrexate, an antimetabolite agent, blocks DNA synthesis<sup>55</sup>, used topically in psoriasis<sup>56</sup> instead of systemically used. If, it is administered systemically causing serious side effects like, bone marrow toxicity, hepatotoxicity, renal impairment, teratogenicity, haematological abnormality, nausea, leucopenia, hepatotoxicity<sup>30</sup>. If methotrexate given topically through micro emulsion or iontophoresis with hydrogels shown good effect in psoriasis<sup>57</sup>.

### **Allantoin**

5-ureidohydantoin, a uric acid derivative, is a product of purine metabolism, prepared synthetically by oxidation of uric acid with alkaline potassium permanganate. Various studies shown that allantoin has keratolytic action and having good efficacy<sup>58</sup>. Allantoin is used along with coal tar.

### **Combination Therapy**

Combination regimens are used in psoriasis therapy because not a single antipsoriatic medication is perfect to treat same. Salicylic acid used along with corticosteroids to increase their penetration as well as efficacy in the treatment of psoriasis but not used in tandem with calcipotriene because calcipotriene is inactivated due to acidic nature of salicylic acid<sup>52</sup>. Tazarotene can be shown good effect in a combination with corticosteroids, when being used once daily at an alternative time<sup>66</sup>.

### **Conclusion**

Topical agents have been applied to human healthcare for immemorial time. Drug discovery in ancient times was largely by coincidence and based on clinical practices. There were wide range of treatment options; there is currently no cure for psoriasis. Topical therapies own the fewest side effects and are booming in treating most patients with limited disease. However, for those who have widespread involvement, disabling disease, more belligerent treatment is required.

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