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Psoriasis: A review

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Abstract
Psoriasis is fundamentally an inflammatory skin condition with reactive abnormal epidermal differentiation and hyperproliferation affecting 2-3 % of world's population. Pathophysiology of the disease includes mainly the activation and migration of T cells to the dermis triggering the release of cytokines (tumor necrosis factor-alpha TNF-alpha, in particular) which lead to the inflammation and the rapid production of skin cells. The possible factors and triggers causing psoriasis include emotional stress, skin injury, systemic infections, certain medications and intestinal upsets. Various types of psoriasis have been reported such as plaque psoriasis, psoriatic arthritis, scalp psoriasis, flexural psoriasis, guttate psoriasis, pustular psoriasis, nail psoriasis, erythrodermic psoriasis which can be diagnosed by clinical findings such as skin biopsies etc. Therapeutic agents that either modulate the immune system or normalize the differentiation program of psoriatic keratinocytes are suggested for treating psoriasis. Based on the type of psoriasis, its location, extent and severity there are various treatment regimens available for psoriasis such as topical agents, phototherapy and systemic agents.

Keywords: psoriasis, plaque psoriasis, psoriatic arthritis, phototherapy, topical steroids

Introduction
Psoriasis is regarded as an autoimmune disease in which genetic and environ mental factors have a significant role. The name of the disease is derived from Greek word 'psora' which means "itch". Psoriasis is a non-contagious, dry, inflammatory and ugly skin disorder, which can involve entire system of person1. It is mostly inherited and mainly characterized by sharply marginated scaly, erythematous plaques that develop in a relatively symmetrical distribution [1, 2]. The most commonly affected sites are the scalp, tips of fingers and toes, palms, soles, umbilicus, gluteus, under the breasts and genitals, elbows, knees, shins and sacrum. This disease is chronic in nature with a tendency to relapse. The silvery-white plaques are caused by accelerated regeneration and accumulation of skin on sites of predilection due to rap id destruction process. Plaques may range in size from a few millimetres to a large part of the trunk or limb. Plaques frequently appear on skin of the elbows and knees, but can affect any area including the scalp and genitals. Fingernails and toenails are frequently affected (psoriaticnail dystrophy) and can be seen as an isolated finding. Psoriasis can also cause inflammation of the joints, which is known as psoriatic arthritis. Psoriasis is linked to dandruff and unfortunately to some forms of arthritis. It is also believed that there is also a link between psoriasis and the HIV virus. Psoriasis is one of the most maltreated diseases from olden days, which continues now with the search of a good remedy. This review is a compilation of all the aspects regarding psoriasis [1, 2].

Causes
The cause of psoriasis is not fully understood, but it is generally believed to have a genetic component. Also in psoriasis, factors in the immune systems and other biochemical substances that normally regulate orderly proliferation and maturation of epidermal cells are impaired. These cause inflammation and increased proliferation of skin cells leading to the characteristic clinical features of scaling and redness. Several factors are thought to aggravate psoriasis. These include stress, excessive alcohol consumption, and smoking. Individuals with psoriasis may suffer from depression and loss self-esteem. As such, quality of life is an important factor in evaluating the severity of the disease. Certain medicines, including lithium salt and beta blockers, have been reported to trigger or aggravate the disease. Excessive alcohol consumption, smoking and obesity may exacerbate psoriasis or make the management of the condition difficult. Individuals suffering from the advanced effects of the human immunodeficiency virus, or HIV, often exhibit Psoriasis. Psoriasis is a fairly idiosyncratic disease [2, 3]. The majority of people's experience of psoriasis is one in which it may worsen or improve for no apparent reason. Studies of the factors associated with psoriasis tend to be based on small (usually hospital based) samples of individuals. These studies tend to suffer from representative issues, and an inability to tease out causal associations in the face of other (possibly unknown) intervening factors. Conflicting findings are often reported. Nevertheless, the first outbreak is sometimes reported following stress (physical and mental), skin injury, and streptococcal infection. Conditions that have been reported as accompanying a worsening of the disease include infections, stress, and changes in season and climate. Researches show that whether a person develops psoriasis or not may depend on a "trigger". Possible psoriasis triggers include emotional stress, skin injury, systemic infections, certain medications and intestinal upsets. Studies have also indicated that a person is born genetically predisposed to psoriasis and multiple genes have been discovered. According to Ayurveda when all these factors combine with change in life style, constipation, indigestion, stress that leads to psoriasis. Stress, skin injuries, a streptococcal infection, certain medications and sunburn are some of the known potential triggers. Medications that can trigger psoriasis are anti-malarial drugs, beta-blockers and lithium. Dermatologists have seen psoriasis suddenly appear after a person takes one of these medications, gets a

streptococcal infection, or experiences another triggers. Sometimes food can also trigger the disease process. For e.g. citrus fruits, sour foods, sauces, coffee, tea, alcohol and soft drinks [3].

Pathophysiology

Psoriasis is immune mediated condition which is caused by faulty signals in the body's immune system. It is believed that psoriasis develops when the immune system tells the body to over-react and accelerate the growth of skin cells. Normally the skin cells mature and are shed from the skin's surface every 28 to 30 days. When psoriasis develops, the skin cells mature in 3 to 6 days and move to skin surface. Instead of being shed, the skin cells pile up, causing the visible lesions. It is also found that genes that cause psoriasis can determine how a person's immune system reacts. These genes can cause psoriasis or other immune-mediated conditions such as rheumatoid arthritis or Type-I Diabetes. The pathophysiology of psoriasis must be understood in terms of the prominent pathologies occuring in both major components of the skin the epidermis and the dermis. There are two main hypotheses about the process that occurs in the development of the disease. The first considers psoriasis as primarily a disorder of excessive growth and reproduction of skin cells. The problem is simply seen as a fault of the epidermis and its keratinocytes. The second hypothesis sees the disease as being an immune mediated disorder in which the excessive reproduction of skin cells is secondary to factors produced by the immune system. Current research suggests that the inflammatory mechanisms are immune based and most likely initiated and maintained primarily by T cells in the dermis. Antigen-presenting cells in the skin, such as Langerhans cells, are believed to migrate from the skin to regionally mph nodes, where they interact with T cells. Presentation of an as yet unidentified antigen to the T cells, as well as a number of co - stimulatory signals, triggers an immune response, leading to T cell activation and the release of cytokines. Co-stimulatory signals are initiated via the interaction of adhesion molecules on the antigen-presenting cells, such as lymphocyte function-associated antigen (LFA)-3 and intercellular adhesion molecule, with their respective receptors CD2 and LFA-1 on T cells. These T cells are released into the circulation and traffic back into the skin. Reactivation of T cells in the dermis and epidermis and the local effects of cytokines such as tumor necrosis factor lead to the inflammation, cell mediated immune responses, and epidermal hyperproliferation observed in persons with psoriasis [3, 4].

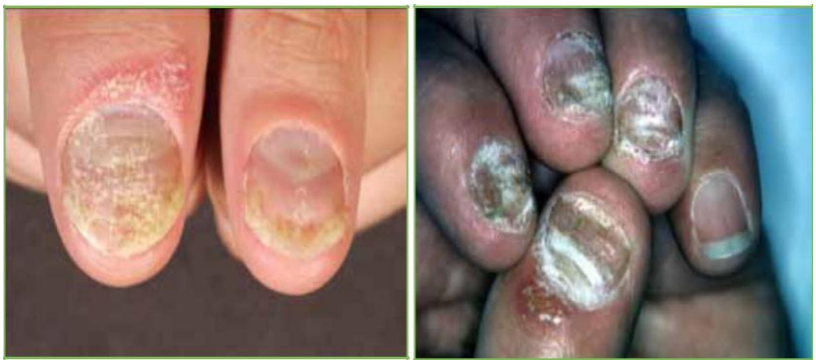

Fig 1: Nail psoriasis

Diagnosis

The diagnosis of psoriasis is usually based on the appearance of the skin. There are no special blood tests or diagnostic procedures for psoriasis. Sometimes a skin biopsy, or scraping may be needed to rule out other disorders and to confirm the diagnosis. Skin from a biopsy will show clubbed Rete pegs if positive for psoriasis. Another sign of psoriasis is that when the plaques are scraped, one can see pinpoint bleeding from the skin below. Diagnosis of psoriasis is made easily by clinical examination. Usually no tests are required to diagnose psoriasis, but to rule out other complications blood tests, urine test and imaging studies are often performed. Sometimes biopsy may be necessary to differentiate it from fungal infection. Blood tests are done for total count, ESSR, RA factor, ASO titre, serum uric acid level, T-cells etc. leukocytosis and increased T-cells lymphocytes are often noted. The microscopic examination of the discharges or blister fluid shows only lymphocytes infiltration. Imaging studies like X-ray or bone scan can help in diagnosing the case with joint pain [4].

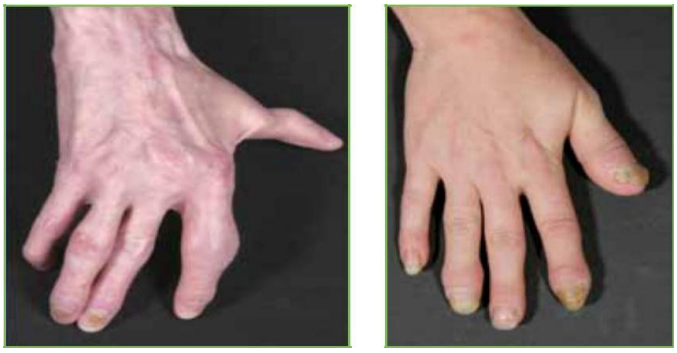

Fig 2: psoriatic arthritis

There are different types of Psoriasis

1. Plaque psoriasis
2. Guttate psoriasis
3. Pustular psoriasis
4. Inverse psoriasis
5. Erythrodermic psoriasis
6. Nail psoriasis
7. Erythrodermic psoriasis
8. Psoriasis of scalp and sole

Table 1: Topical treatment for psoriasis [4]

Drug	Formulation	Disease Type
	Monotherapy	
Corticosteroids		
Clobetasol propionate	Ointment, spray, foam, lotion,	Plaque and scalp psoriasis
	Shampoo	
Halobetasol propionate	Ointment	Plaque psoriasis
Betamethasone	Cream, gel, lotion, foam	Plaque and scalp psoriasis
Mometasone	Cream, ointment, gel	Plaque and scalp psoriasis
Vitamin D3 analogues		
Calcipotriol	Ointment, cream, solution	Plaque, scalp and nail
		Psoriasis
Calcitriol	Ointment	Plaque psoriasis
Tacalcitol	Ointment	Plaque psoriasis
Retinoids		
Tazarotene	Gel, cream	Plaque psoriasis
Coal tar	Ointment, gel, solution, shampoo,	Plaque and scalp psoriasis
	Soap	
Anthralin	Ointment, cream	Plaque psoriasis
Calcineurin inhibitors *(investigational use)*		
Tacrolimus	Ointment	Face, genitelia and
		intertriginous psoriasis
Pimecrolimus	Cream	Intertriginous psoriasis
PDE4 inhibitors		
AN-2728	Ointment	Plaque psoriasis
	Combination Product	
Calcipotriol +	Ointment	Plaque, scalp and nail
Betamethasone		Psoriasis
Dipropionate		
Betamethasone	Ointment, cream, lotion	Plaque, scalp and nail
dipropionate + salicylic		Psoriasis
Acid		

Guidance for effective management of psoriasis

Although there is no cure for psoriasis, several available therapies can help control skin lesions and associated symptoms. Some treatments can also induce remission for months or longer. Despite availability of numerous topical and systemic treatment options, there is a lack of patient satisfaction with the available treatments and high rates of non-compliance. In order to optimize topical treatment of psoriasis, guidelines have been developed for more effective management of psoriasis. Some of the available guidances for topical treatment are discussed in this section:

The American Academy of Dermatology (AAD) has published a six part series of guidelines in 2009, on the management of psoriasis and psoriatic arthritis. The third section of this series discusses the use of topical medications for the treatment of psoriasis (Menter *et al*., 2009). This guidance discusses the efficacy and safety of as well as offer recommendations for the use of topical corticosteroids such as vitamin D analogues, tazarotene, tacrolimus, pimecrolimus, emollients, salicylic acid, anthralin, coal tar, as well as combination therapy. The authors concluded that patients with localized psoriasis can be treated with topical agents, which generally provide a high efficacy-to-safety ratio. Topical agents may also be used adjunctively in patients with more extensive psoriasis who are undergoing therapy with either ultraviolet light, systemic or biologic medications. However, the use of topical agents as monotherapy in the generalized form of the disease or in the setting of limited, but recalcitrant, disease was not recommended [4, 5].

The Cochrane Skin Group in UK published a review of topical therapies for chronic plaque psoriasis following examination of 131 studies (Mason *et al*., 2009). They concluded that vitamin D analogues showed similar efficacy as potent or very potent corticosteroids when used on the body, whereas topical corticosteroids proved the most effective treatment for scalp psoriasis. Combination of topical corticosteroids and vitamin D analogues were more effective than either agent as single formulation. Although the overall safety of topical therapies was high, topical corticosteroids were associated with lower incidence of local adverse events than vitamin D analogues. Warren *et al.* (Warren *et al*., 2010) has published a review summarizing the guidances on the use of topical, systemic and biological therapies for the treatment of psoriasis; co-morbidities associated with psoriasis; and complementary therapies for psoriasis. The UK National Health Service provides an annual evidence update on psoriasis and has included new guidelines and systematic reviews on psoriasis published or indexed from November 2008 to October 2009 in

the 2009 Annual Evidence Update on Psoriasis from NHS Evidence – Skin Disorders [5].

Other topical treatment

Phototherapy

It has long been recognized that daily, short, non - burning exposure to sunlight helped to clear or improve psoriasis. Niels Finsen was the first physician to investigate the therapeutic effects of sunlight scientifically and to use sunlight in clinical practice. This became known as phototherapy. Sunlight contains many different wavelengths of light. It was during the early part of the 20th century that it was recognized that for psoriasis the therapeutic property of sunlight was due to the wavelengths classified as ultraviolet (UV) light.

Phototherapy involves exposure to ultraviolet radiations by means of special equipment using fluorescent light source emitting specific wavelength of radiation. Natural sunlight may be used as a source of UV, but exposure becomes imprecise. UV acts by reducing cellular proliferation and modifying the immune response. Psoriasis responds to ultraviolet rays. Regular exposure to sun or artificial UV lights can cause the symptoms to subside. Approaches include UVB i.e. exposure to UV B light and PUVA i.e. exposure to UV rays combined with the drug psoralen, which increases the light sensitivity of skin. New techniques include lasers, which can focus the beneficial effects of light especially on psoriatic lesions. UV phototherapy is the simplest and easiest treatment with the best general results for clearing psoriasis [5].

- UVB therapy: Ultraviolet B is widely used as broadband therapy (290-320n m). Now-a days narrow band UVB (310-312n m) has become more popular either as a sole agent or in combination with topical calcipotriol or tazarotene, or systemic agents like acetretin or methotrexate. Narrow band UVB therapy is a relatively safe and effective therapy for moderate to severe psoriasis. UVB treatment initially takes place with a doctor, but UVB units are also available for use in the home. UVB works by stimulating a chemical reaction in the skin cells to stop them reproducing so quickly.
- PUVA therapy: Ultraviolet A (320-400n m) is used in combination with a photosensitizing agent. A psoralen compound (usually 8-methoxy psoralen i.e., 8MOP) is taken orally followed by exposure to UVA (PUVA therapy = Psoralen + UVA). The usual dose is 0.6mg/kg taken two hours before exposure. Exposure time is gradually increased till adequate response is obtained. Two or three treatments are given per week. Protective sunglasses should be worn during exposure and for the remainder of the day. After significant clearance of the lesions, frequency of administration is reduced and maintenance treatments continued for a variable period [5, 6].

Systemic treatment

Psoriasis which is resistant to topical treatment and phototherapy is treated by medications that are taken internally by pill or injection. This is called systemic treatment. Patients undergoing systemic treatment are required to have regular blood and liver function tests because of the toxicity of the medication. Pregnancy must be avoided for the majority of these treatments. Most people experience a recurrence of psoriasis after systemic treatment is discontinued. The three main traditional systemic treatments are methotrexate, cyclosporine and retinoids. Methotrexate and cyclosporine are immunosuppressant drugs; retinoids are synthetic forms of vitamin A. other additional drugs, not specifically licensed for psoriasis, have been found effective. These include the antimetabolite tioguanine, the cytotoxic agent hydroxyurea, sulfasalazine, the immunosuppresents mycophenolate mofetil, azathioprine and tacrolimus. These have all been used effectively to treat psoriasis when other treatments have failed. Although not licensed in many countries fumaric acid esters have also been used to treat severe psoriasis in Germany for over 20 years. Various oral and injectable drugs are used in severe disease not responding to topical agents. Generally, these drugs have potential for serious adverse effects. Oral medications such as methotrexate and cyclosporine may help. Systematic therapy as a variety of oral or injectable medications is used in severe recalcitrant psoriasis in adults. Some of them may be combined for better efficacy. All these agents are potent medicines with potential for serious toxicities. They should be used in only extreme situations in childhood psoriasis. Many of these drugs have potentially severe side effects. You will need to be monitored closely when using them [7, 8].

- Methotrexate: This anti-metabolite is a very popular and effective agent for treating severe psoriasis. It is usually given in a weekly or occasionally fortnightly pulse of 15mg. Equivalent dosage may also be used by intra-muscular or intravenous route. Methotrexate is effective in psoriatic arthropathy also. A low dose of maintenance therapy may be continued for sometime before withdrawal of the drug. Methotrexate schedule, the drug is remarkably well tolerated. Common side effects include anorexia, nausea and epigastric pain [8].
- Oral retinoids: These are synthetic compounds having Vita-A like cellular activities. A number of retinoids are available for treatment of severe forms of acne or other disorders of keratinization. Among them, acetretin is useful in the management of psoriasis. Oral retinoids act by their anti-inflammatory actions as well as by regulation and maturation. Acetretin is most effective when combined with topical agents or phototherapy in the generalized pustular and erythrodermic varieties of psoriasis. All retinoids have potentially serious toxicities. The most important is the risk of birth defects. So pregnant women or women who intend to become pregnant should never receive oral retinoids. Strict contraceptive methods should be done. Skin and mucous membrane side effects are common in the form of dryness of skin, nose, eyes, chapped lips and peeling of palmoplanter skin. Regular monitoring of lipid profile is needed [9].
- Cyclosporine: It is a cyclic polypeptide widely used as an immunosuppressant in organ transplantation. It acts in psoriasis through its inhibitory effects on T-cells. Cyclosporine should be reserved for patients with severe psoriasis. The usual oral dose is 3-5mg/kg in two divided doses. Major side effects are nephrotoxocity and hypertension. It may increase the risk of malignancies. It is contraindicated in renal dysfunction, hypertension, past or present malignancies, pregnancy, lactation and concomitant therapy with immunosuppressive or nephrotoxic drugs, this agent, like oral retinoids should be administered by dermatologists having experience in its use [10].

Table 2: Some of the synthetic drugs with category given below

Drugs and Category	Trade Name	
Acitretin (Retinoid)	Acerate (10mg),	Acetec (25mg),
	Zerotem (25mg)	
Alefacept (Immunosuppressant)	Acnethro (50mg), Aloederm - B,	
	Aloederm – D (250gm)	
Allantoin (Topical agent)	Ointment anomex clenchin – 3	
Anthalin (Anti - miotic)	Cozen (15mg, 20mg)	
Hydroxy urea (Antineoplastic)	Cytodrox - D	urea, Hondria,
	Niodria	
Infliximab (Monoclonal Antibody)	Remicade	

Alternative Natural Treatments for Psoriasis

The herbal medicines not have more side effects as compared to synthetic drugs. The herbal medicine is easily available and easy to use in treatment. Now a day, herbal resources play a very important role in the management of the skin and inflammatory diseases. Some studies suggest that psoriasis symptoms can be relieved by change in diet and lifestyle. Fasting food period, low energy diet and vegetarian diets have improved psoriasis symptoms.[10,11] In some treatments supplemented with fish oil shows a beneficial effect due to the presence of omega - 3 Fatty Acids and Vitamin E. Cannabis is also suggested for treating psoriasis due to Anti - inflammatory properties of its canabinoids and their regulatory effect on immune system (Bhuchar *et al*., 2012, Brown *et al*., 1998, Brown *et al*., 2004; Farber *et al*., 1986; Koo *et al*., 1998, Mantle *et al*., 2001; Deng *et al*., 2013). Some herbal alternatives for natural psoriasis treatment and the possible rationale of their anti-psoriatic activity have been discussed below briefly on the basis of reports of some researches [12, 13].

Table 3: Showing Plant Name, Family, Local Name and Plant Parts Used [13, 14, 15]

S. No.	Botanical name	Family name	Common name & Local name	Plant parts used
1	*Aloe vera*	Liliaceae	Aloes, Kathalai	Leaf
2	*Alpinia galangal*	Zingiberaceae	Thai Ginger, akkulati	Rhizome
3	*Angelica sinensis*	Apiaceae	Chinese angelica	Root
4	*Andrographis nallamalayanna*	Acanthaceae	Echinacea, Siriyaa Nangai/Nila Vembu	Whole plant
5	*Annona squamosal*	Annonaceae	Sugar Apple, Custardapple Sitapalam	Rhizome and leaf
6	*Argemone mexicana* L.	Papavaraceae	Mexican Prickly Poppy Kudiyotti	Root
7	*Azadirachta indica* A. Juss.	Meliaceae	Neem, Veppam	Leaves, bark and
				Stem

New Treatments for Psoriasis

- Anti-TNF Treatments- Anti-TNF- has been developed to capture the TNF- and to block its activity and consequently reduce the interactions between immune cells and keratinocytes. There are different molecules inhibiting TNF- in the treatment of psoriasis. Currently, there are three TNF- inhibitors that are approved for treatment. The neutralization of the TNF- prevents its interaction with receptors TNFR1. The binding of the TNF- at the receptor level results in a cascade of pathways. This process is then used to activate the NF-KB1 which is a transcription factor that induces proliferation, cell survival, and cytokine production [16-18].
- Other Anticytokines Treatments- It is known from the literature that Th17 cells and IL-23 are important in the development of psoriasis. IL-23 stimulates the survival and the proliferation of immune cells. In an individual with psoriasis, the production of IL-23 is increased by the dendritic cells and macrophages and is important for the development and maintenance of Th17 cells [18-20].
- Anti-T Cells Treatment- This molecule has been developed specifically to modify the inflammatory process triggered with psoriasis. This molecule specifically inhibits T-cell activation. The LFA-3 molecule is expressed on antigen-presenting cells. During the formation of the immunological synapse, it will bind to CD2 molecules expressed on mature T-cells and natural killer cells (NK). The binding of LFA-3 with CD2 molecule will generate important costimulatory signals in the process of naive T-cell activation in effector cells. Psoriatic lesions contain mainly memory T-cells (CD45RO +) [21, 22]
- Small Molecule Inhibitors-This phosphodiesterase (PDE) plays a key role in the degradation of adenosine monophosphate (AMP) in cells. Inhibitors of phosphodiesterase will help prevent T-cell secretion of inflammatory cytokines such as TNF- or IFN- and IL-2 from peripheral blood monocytes and T cells. There are eight families of PDE, of which the PDE4 family is the most prevalent in immune cells and is expressed by keratinocytes. Inhibition of PDE4 increases the intracellular concentration of cyclic adenosine monophosphate and subsequently reduces the production of proinflammatory cytokines [24, 23].
- Nerve Growth Factor Inhibition- Research shows that there may be a link between emotional stress, the peripheral nervous system, and the onset of psoriatic lesions. More precisely, during stress, sensory nerve fibers release neuropeptides in large quantities. Psoriatic lesional and non lesional plaques contain a large amount of nerve growth factor (NGF) which plays a role in keratinocyte proliferation, angiogenesis, T-cell activation [25, 26].

Conclusion

Psoriasis is a dreadful disease affecting physical, mental and social status of the victims. A new understanding of this complex disease has catalyzed the development of targeted biological treat ments. These revolutionary therapies are not without potential risk, however. A review of alternative natural

therapies provides some options for increasing safety and efficacy in the management of psoriasis. This review will surely prove to be an eye-opener for patients suffering from psoriasis as well as the medical practioners, pharmacists, nurses and other persons involved in the treatment of psoriasis and help them to understand the disease in a much better way to carry out safe and effective treatment of the disease.

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