AMJ
ISSN: 0005-2523

ISSN: 0005-2523
Volume 62, Issue 08, December 2022

A REVIEW ON THE ROLE OF NATURAL REMEDIES USED IN PSORIASIS

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Abstract

Psoriasis is a chronic inflammatory disorder that affects more than 100 million people globally. It is not just a cosmetic disease since it creates a huge impact on an individual's lifestyle. It shows symptoms such as red inflamed and flaky patches on the skin. Psoriasis is said to be a multifactorial disease since it is caused mainly due to genetic and environmental factors such as stress, heavy alcohol consumption, infections such as strep throat, and also due to medications such as beta-blockers, antimalarials, lithium, etc. It is a well-known fact that conventional medications cannot be afforded by everyone and also causes toxicities, there is a need for alternative methods of treatment. Studies have found that many herbal medicines show antipsoriatic properties which can be used as alternatives in the treatment of the disease.There is no long-term treatment for the autoimmune illness and inflammatory condition known as psoriasis. An inflammatory, dry, and non-contagious skin condition is psoriasis. Different areas of the skin are affected by psoriasis, which is characterized by sharply scaly, erythematous plaques. Genetic, environmental, and immunological factors all contribute to the reasons. There are many different therapies on the market, some of which are pricey and have several adverse effects. Psoriasis is diagnosed with natural plants in Ayurveda. The elements and doshas are factors in ayurvedic medicine. The potential for anti-psoriatic action of herbal drugs is due to their safety and accessibility. Investigating proliferative activity is psoriasis. Herbal resources create a powerful, secure, and dependable treatment. In this review, different pathophysiological models used for the screening of psoriasis have been summarized along with various medicinal plants that are proven to have antipsoriatic properties.

Keywords: Psoriasis, Screening models, Herbal medicines, Disease

Introduction

Psoriasis is a type of immune destructive disorder that causes a rapid escalation of skin cell layers. Its histopathological characteristics include epidermal hyperplasia which is the abnormal differentiation of skin layers, parakeratosis, hyperkeratosis, reduced or absence of granular layer, infiltration of inflammatory CD4+ and CD8+ T-cells, CD11c+ dendritic cells in the dermis and neutrophils are found in the epidermis. Apart from this, an increase in the formation of blood vessels is also observed. [1, 2]

It is differentiated as Plaque, Guttate, Erythrodermic, Pustular and Inverse Psoriasis. Among these, the prevalent form is Plaque psoriasis also called Psoriasis Vulgaris. It is identified by red inflamed patches, whitish-silvery scales on the patches, and dry skin which may sometimes itch or burn.This is the most common type of Ps since it represents approximately 90% of the cases. The patches

are mostly found on the knees, elbows, scalp and sacral regions. Guttate psoriasis is linked with the HLA-Cw6 gene and can be distinguished by small round and circular droplets[3]. These droplets are also called papules which are found on the torso, hand, armpits, face, legs, etc. It is generally seen in children and young adults. 8% of the people with the disease develop guttate psoriasis since it is the 2nd most prevalent form. It is generally caused due to infections such as strep throat and other triggers such as injury to the skin, tonsillitis, drugs such as antimalarial and beta-blockers. Erythrodermic Ps is a rare condition that comprises severe skin redness over a large part of the body, shedding of the skin in large sheets, severe itching, pain, fluctuations in body temperature and an increase in heart rate is observed. It leads to protein and fluid loss leading to illness. Edema can also occur due to retention of fluids around the ankles. This is associated with other alarming diseases such as pneumonia and CHF, cardiovascular shock or septic shock.Pustular psoriasis a very rare condition that is associated with raised blebs on the skin filled with pus. The pus consists of WBCs which is noninfectious. It generally affects young individuals and it is triggered by certain internal medications, stress, systemic steroids, irritating topical agents, etc. Inverse or flexural psoriasis are characterized as red, shiny patches found in the skin folds of the body i.e. in the armpits, around the genitals, between the buttocks, and under the breasts. [3] These psoriatic lesions can sometimes cause fissures that can bleed and burn in turn causing severe pain. In serious conditions, these can develop into Psoriatic Arthritis (PsA). The average male to female ratio of PsA is 1:1. [3] The disease can be treated by topical agents, systemic drugs or phototherapy. Topical corticosteroids such as betamethasone, triamcinolone, and vitamin D analogues i.e. Calcipotriene, etc. are prescribed for mild to moderate psoriasis since it slows down the skin cell growth. Systemic medicines such as methotrexate, cyclosporine, acitretin are given orally whereas as adalimumab, etanercept, infliximab, ustekinumab are administered through i.v. route in cases of moderate to severe psoriasis. Phototherapy includes exposure to sunlight (UV rays), broadband UV therapy or UVB phototherapy, narrow band UVB phototherapy, PUVA (PsolarenPlus Ultraviolet A), etc. Even though these drugs produce required effects, it has been noted that systemic medicines such as methotrexate produces hepatotoxicity and cyclosporine produces nephrotoxicity whereas phototherapy can lead to long term cutaneous malignancies. Hence there is a need for alternative methods of treatment with lesser-known side effects and studies have revealed that herbal medicines have potential as an alternative treatment for psoriasis. This review focuses on the different types of pathophysiological models available for the screening of the disease to develop drugs that can reduce its symptoms. These models are induced with psoriasis-like characteristics which are isomorphic to humans and tested with the active principle of the herbal medicine known to have antipsoriatic property.

Global Statistics

The disease is a globally occurring phenomenon which has largely affected millions of people around the world. According to the statistics of the Global Report on Psoriasis by the World Health Organization (WHO), it was recorded that Ps occurs most commonly in Northern Europe and least in Eastern Asia. A study conducted in 2001 in the USA among Caucasians, Blacks, and others

showed that there was a disease prevalence of 2.5%, 1.3%, and 1% respectively. Another study conducted in the USA in the year 2009-2010 among the populations of Caucasians, blacks, Hispanics and others showed that the disease prevalence was 3.6%, 1.9%, 1.6%, and 1.4% respectively. The statistics of both these studies varied by a large percentage showing the increase in the occurrence of the disease over the years. It was also observed that the Caucasians were among the largely affected population in the USA. Generally, both men and women are equally affected but some studies show that it is more prevalent in men than in women, also the disease is not age-specific as it can occur at any age. Most studies show that it occurs by the age of 20-30 or after 50yrs but it can even affect children well before 20. When a person gets this disease, it impacts their life majorly in all aspects. A study conducted in the USA on how Ps impacts a person's daily life was studied and the following statistics were obtained.

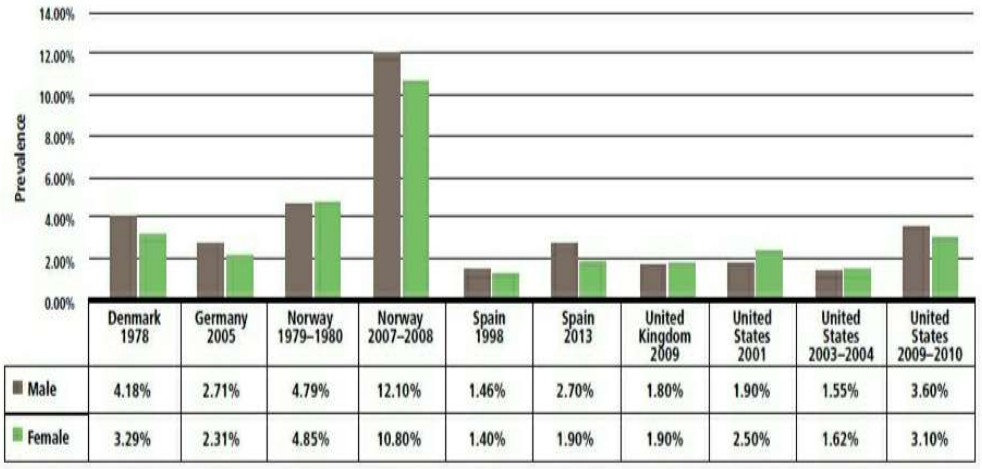
PATIENTS		IMPACT ON
98%	-	Emotional life
94%	-	social life
70%	-	Family
68%	-	Professional career
38%	-	Physical functioning
21%	-	Educational life
17%	-	Sexual intimacy

Due to the change in lifestyle and quality of life, the disease has progressed a lot over the years. Prevalence of the disease was studied in china in the year 1984 and was found to be 0.17% which increased to 0.59% in 2009, in Spain the prevalence was 1.43% in 1998 which got increased to 2.31% in 2013, a 30yr follow-up study conducted in Norway showed a prevalence of 1.62% in the year 1979 which increased to 3.10% in 2010.[3]

The table below represents studies on the widespread presence of Psoriasis in all age groups.

Geographic location	Year(s) of study	Sample size	Estimate	Female	Male	Ages of subjects
China, Taiwan	2005	3237	0.00%			6-11
Egypt	2011-2012	6162	0.06%			6-12
Germany	2007	1,215,684	0.40%	0.44%	0.35%	<18
Germany	2009	293181	0.45%			<18
Italy	2012	145233	0.2%			0-14
Sweden	1975-1976	8298	0.30%	0.50%	0.10%	12-17
Australia	1997-1998	1457	6.6%	4.5%	8.9%	>20
United kingdom	…	58257	1.3%			18-64
United states of	2011	799607	0.51%-			>65

America			1.13%			
China	2006	23 000 000	0.235%			All ages
Japan	2010–2011	128 000 000	0.44%			all ages
Norway	1991	2 508	1.40%			all ages
Spain	2013	12 711	2.31%	1.9%	2.7%	all ages
United Kingdom	2009	7 520 293	1.87%	1.9%	1.8%	all ages
United States of America	2009	2573	5.1%			all ages



The graph aboverepresents prevalence of Psoriasis by sex.[3]

Prevalence studies in India were also performed which were mostly hospital-based. Okhandiar et al. collected data from medical colleges in north-eastern states which showed an overall incidence of 1.02%. It showed that Amritsar had the highest incidence of 2.2% as compared to other places in North-Eastern India.[4] A study conducted by Bedi et al. in North India with 162 patients showed a prevalence of 0.8% with less number of subjects.[5] Another study conducted by Bedi with 530 subjects showed a prevalence of 2.8%. Prevalence in India varies from 0.44% to 2.8% and also found to be more common in men.[4]Kaur et al.,

No. of Patients	Prevelance
3573	1.02%
162	0.8%
530	2.4%
1220	2.3%

carried out a study with 1220 patients suffering from psoriasis showed a prevalence of 2.3%.[6]However, the occurrence of Ps varies according to an individual's age, region and

ethnicity, environmental and genetic factors. In the USA there is a record of 7-8 million people being affected by this disease and it was also observed that majority of the people with Crohn's disease and ulcerative colitis are more prone to suffer from Ps. [7]

Physiology

Psoriasis is a chronic skin disorder that can be multifactorial i.e. can be caused by genetic and environmental factors. It is a debilitating disease which is caused by immune disregulation leading to increased keratinocyte production and psoriatic plaque. Although the exact cause for immune disregulation is not known. Studies have found that dendritic cells, T lymphocytes, macrophages, neutrophils, keratinocytes, and some specific cytokines are present in the active state as infiltrants. The antigen on the skin activates dendritic cells in places such as lymph nodes and interacts with naive T-cells, these then transform into activated memory T-cells which then differentiate into effector cells such as Th1, Th2, and Th17. Each of these effector cells travels through the circulation to the site of inflammation and is responsible for the release of cytokines such as TNF-α, INF-γ, and IL-2 which also plays an important role in the inflammatory cascade. This leads to keratinocyte proliferation and psoriatic plaques. TNF-α helps in the development of lesions by increasing the number of molecules involved in the inflammatory response.[2]Activated keratinocytes release chemokines which are responsible for bringing the lymphocytes to the site of inflammation. Besides, dendritic cells release cytokines IL-12 and IL-23 which contributes to the activation of T-cells. Increased vascularization and inflammation are observed due to angiogenesis which is because of higher production of vascular endothelial growth factor (VEGF) in epidermal keratinocytes. Studies have also shown that cytokines such as IL-8 causes infiltration of neutrophils in the skin. [2]Researchers believe that a more thorough understanding will provide insights into the prevention and treatment of the disease.

In Vivo Screening Models

Evaluation of a drug's biological activity as a whole, living organism mainly animals and humans are termed as in vivo studies. Animal models are the main key components for testing the drugs designed for the treatment of diseases. In order to run tests on the animal models, there should be pathological and immunological similarities with the human body. To date, there is no animal model that has similar characteristics of psoriasis as that of humans.

For it to be considered as a perfect in vivo screening model it should have the following characteristics: [8]

1) Increased vascularization
2) Analogous tissue pathological images
3) A similar mechanism of disease
4) Presumable response to drugs used in Ps
5) Similar etiology
6) Reproducible
7) Inexpensive

8) Compatible with ethical considerations
However, the models did not fit according to the above criteria, they were rather used to study other mechanisms such as thickening of the skin layers, modulation of neutrophil infiltration, and micro abscess formation or dermal angiogenesis. [9]

Homozygous asebia mouse (*Scd1*^{ab}/*Scd1*^{ab})

These mutant mice were the first in vivo models and were used mainly to study hyperkeratotic disorder. Gates et al. discovered that due to an autosomal recessive mutation in the BALB/c strain of mouse, absence of sebaceous glands, hyperkeratosis, alopecia, and single hair-follicle units occurred spontaneously hence, they named these mutations asebia. Studies revealed that normal skin grafts restore normal hair growth and prevent hyperkeratosis. [10] On further discovery by Brown et al., on asebia mouse, it was found out that the mouse showed excessive epidermal thickening (16.5+ 1.5 μm; $P < 0.0005$), increase in the number of mast cells, macrophages, and fibroblasts. [11]Zheng et al., discovered that the underdevelopment of sebaceous glands resulted in a defective Scd-1 gene (stearoyl coenzyme A desaturase 1).[12]This model showed almost all the characteristics similar to Ps but lack of T- cells and neutrophils does not resemble the psoriatic lesions and alteration of cutaneous lipid metabolism seems different from Ps. [9]

Flaky skin mice (Ttcfsn/Ttcfsn)
Sundberg et al., observed that in the fsn mutant mouse model, inflammatory cells were found both in the dermis and the epidermis along with the substantial amount of mast cells, neutrophils, and macrophages. Studies showed elevation on the surface of the skin due to hyperplasia in the stratified squamous epithelium of the forestomach. [13]This model was believed to be useful for the screening of the disease since its characteristics were considered isomorphic to the human psoriatic phenotype, until Schon et al., in 2000 observed that it could only deplete the levels of neutrophils as well as markedly diminish the extent of epidermal acanthosis, hyperproliferation, and cutaneous T-cell infiltration whereas, mast cells and MHC class II+ epidermal dendritic cells were not affected on injecting neutrophil depleting monoclonal antibody. [14] Later in 2001, studies found out IL-β1 cytokine plays a major role in the disease progression since it was found to be overexpressed within the psoriasiform skin lesions. When the inflammatory biomarker was inhibited, epidermal acanthosis, hyperproliferation, cutaneous T-cell and neutrophil infiltration and dendritic cells noticeably declined still there was no effect seen on the increased levels of mast cells.[15]Therefore, this model could only be useful for studying local events characterizing hyperproliferative inflammatory skin changes.[14]

Spontaneous chronic proliferative dermatitis mutation(Sharpincpdm/Sharpincpdm)
This model also had the same drawback as in the flaky skin mice model. The lack of T-cell based immunopathogenesis and no response to immunosuppressive agents caused a limitation in the research. [16]

Genetically Engineered Models

This category consists of a large number of psoriatic screening models eg. Transgenic and knockout models.

HLA-B27 rat

This genetically engineered rat has been developed which directly targets the immune system. Hammer et al., discovered that humans who have inherited the MHC class I HLA-B27 allele have a higher risk of developing spondyloarthropathies one of which is psoriatic spondylitis. B27 and human β2 microglobulin were introduced into rats to study the role of B27 in the inflammatory diseases.[17] The rats developed epidermal thickness, dystrophy of the nails, thickened rete ridges, infiltration of neutrophils, leukocytes, presence of activated α/β T-cells, CD4 and CD8 T-cells and plasma cells.Apart from this the B27 transgenic rat also consists of differentiating features such as thick suprapapillary plates, less prominent rete ridges, absence of atrophy in sebaceous glands which is commonly seen in the diseased state.This model also confirms that there is a T-cell or keratinocyte mediated cytokine production which is responsible for the skin lesions.[18]Even though this model has certain mechanisms resembling the human psoriasis it hasn't gained much prevalence as the model of choice.

CD-18 HYPOMORPHIC

This was developed to directly target the leukocytes. [1] Bullard, et al crossed the mutated mice with the PL/J strain of the mice it develops a psoriasiform phenotype with epidermal hyperplasia, hyperkeratosis, parakeratosis, sub-corneal microabscess, infiltration of leukocytes and dilation of dermal capillaries. When treated with dexamethasone there was an improvement in the condition. [19] Studies found out that for the generation of the above characteristics the CD18 expression must be decreased as seen in human psoriasis. [20, 21] On the other hand, Kess et al., also discovered that for psoriasiform dermatitis to occur CD4+ T-cells are much more mandatory than the CD8+ T-cells. [21] Hence this model proves to be of much importance and can be considered as a model worth use for future experiments.

K-14/VEGF and Tie 2

Xia et al., discovered that the K14-VEGF mice model develops pre psoriatic phenotype such as epidermal hyperplasia, nucleated keratinocytes in the stratum corneum, mild rete ridge formation, increase in mast cells and macrophages, enormous levels of CD4+ T-cells at 3 months of age. It further showed a fully developed rete ridge and cutaneous inflammation at 5 months of age. Studies also revealed that there was an increased expression of K6 in the transgenic mice. This study reveals that overexpression of VEGF over time gives rise to characteristics very similar to human psoriasis. [22]

The Tie-2 transgenic mice had the same characteristics as that of the K-14/VEGF mouse model. It was discovered that on activation of the transgene it shows erythema with silver-white scaling, hyperkeratosis, parakeratosis, angiogenesis, infiltration of inflammatory cells and

neutrophilicmicroabscess. The only difference in this mouse model was that it showed a therapeutic response to cyclosporine A. [23, 24]

K14/TGF-α, K14/KGF, K5/TGF-β1

Vassar and Fuchs used human keratin K14 promoter to target the expression of TGF-α on the stratified squamous epithelia of the transgenic mice. The results revealed a marked difference between juvenile K14- TGF-α and the human psoriatic skin since there was no proof of major inflammatory response in the young transgenic mice i.e. signs of gross leukocytic infiltration. Although the adult transgenic mice showed signs of leukocytic infiltration and granular layer loss, which is similar to the human psoriatic phenotype. Since TGF-α is considered as the major determiner of epidermal thickness during the growth and development stage, it is believed that human psoriatic skin must express a high level of this biomarker and hence needs further study. [25] Similarly Guo et al., performed an experiment targeting the KGF in the stratified squamous epithelium using the same K14 promoter and it was found that apart from the changes observed in the study made by (Vassar and Fuchs 1991), impairment in the submandibular gland development and excessive saliva secretion were also observed which revealed differences between KGF and TGF- α. [26] Yet another experiment by Li et al., revealed that TGF-β1 inhibits keratinocytes i.e. when keratinocyte hyperproliferation occurs there are decreased levels of TGF- β1. Hence a transgenic mouse was produced by targeting TGF-β1 on the epidermis of the mouse using keratin 5 (K5) promoter. It was observed that the mouse developed skin inflammation, psoriatic lesions, and erythematous plaques and with the progression, in the age of the mouse, it further exhibited infiltration of the inflammatory cells, vasodilation, and angiogenesis. [27] Also, it was found that TGFβ1 and PASI are correlated and it is considered as an indicator of the disease signs are positive. [28] All these characteristics were similar to human psoriatic lesions. Although there are a few factors that prove that this model cannot be considered as the best model to study the disease because the model does not cure the inflammation on the skin with IL-23 treatment and the role of T-cells is only limited to the initial stages of this model. Hence it is evident from the above data that TGFβ1 overexpression alone is not adequate to imitate all the functions of psoriasis. [29]

K5.Stat3C

This model was designed using the K5 promoter by targeting Stat3 in the epidermal keratinocytes. This factor leads to various biological activities including gp130 mediated cell proliferation, survival, and cell migration. [30] The histological characteristics include acanthosis with elongated rete pegs, retention of nuclei in the stratum corneum, absence of granular layer, infiltration of inflammatory cells, vasodilation and angiogenesis. It was also observed that lesions kept on spreading which worsened on aging. The studies revealed that activated Stat3 and T-cells both are necessary for psoriasis-like lesions to develop. [31]

Xenotransplantation

This type of animal model is developed by obtaining the biopsied human psoriatic skin or

developing skin in vitro with similar characteristics as that of humans and its transplantation on the recipient transgenic or spontaneously mutated mouse model. In most of the xenotransplantation experiments, Severe combined immunodeficient mouse models were used as transplant recipients. The SCID model lacks T and B-cells due to alterations in the DNA dependent protein kinase (DNA-Pk) enzyme encoded by the PRKDC gene. Since mature NK cells are present in the model, it rejects single-cell suspensions, but it was observed that it accepts the solid tissue grafts from the human psoriatic skin. [32, 23] Yet another model was developed by grafting pre-symptomatic psoriatic skin on the AGR129 mice. This mouse also lacks T and B cells in addition to the presence of immature NK cells with impaired cytotoxic activity.

It was observed that phenotypic conversion occurred at week 4 and got fully developed after 6-8 weeks of engraftment. The results showed that T-cell proliferation reaches a max in 4 weeks which coincides with an almost five-fold increase in the tissue. Therefore to prove T-cells play a major role in the development of psoriatic phenotype, monoclonal anti-human CD3 antibody muromonab CD3 (OKT3) was injected into the mice and proliferation of T-cells was terminated which caused a decrease in the psoriatic phenotype. [33] Hence it was noted that for the maintenance of psoriatic phenotypes the infiltration of T-cells is necessary and that inflammatory cells cause the condition of psoriasis. [34]

Direct Induction

Imiquimod induced mouse model was produced by application of imiquimod topically on the BALB/c mice and it was observed that the mouse developed erythema, scaling and thickening after 3 days of application. Daily application of IMQ led to psoriatic plaques, increased epidermal growth and differentiation, erythema, altered vascularity, neoangiogenesis, an influx of inflammatory T-cells (CD4+) and CD11c+ dendritic cells. By RT-PCR analysis it was observed that IL-23 levels have increased followed by increased expression of IL-17A, IL-17F, and IL-22. It was observed that the psoriatic characteristics are partially blocked in mice deficient with IL-17 and IL-23. Hence this establishes a reason that IL-17 and IL-23 are important cytokines for psoriasis to occur. [35]

Since both macrophages and plasma dendritic cells (pDCs) express Toll-like receptors (TLR-7), they are considered as potential targets of IMQ. Based on the observations made by Gilliet et al., it was found that there are large no. of PDCs in human psoriatic skin lesions. [36] In a study by Ueyama et al., tlr7 mice were used to determine whether IMQ induced inflammation is mediated through TLR7. The drug was applied topically on the mice and it was observed that the skin inflammation had decreased along with the epidermal thickness of the skin. IL-17, IL-22 and IL-23 expression had decreased. These results established the fact that IMQ induced inflammation was mediated via the IL-23/Th-17 pathway via TLR-7. It was also noted that the application of IMQ can also induce the production of IL-6, IFN-α, IL-23, and TNF- α via TLR-7 from PDCs present in the skin in vivo. Even though this model needs further investigation to be carried out, it can be used to study the disease pathogenesis. [37]

In Vitro Models

Researchers developed models that could be studied outside the body of an animal using cells or tissues providing all the physiochemical and biological conditions. Since the in vivo approach could not generate a suitable model with all the characteristics of Ps, researchers produced models in vitro taking a biopsy of psoriatic human skin and generate epidermal keratinocytes in human cell lines or tissues to mimic the characteristics of the disease.

Since the monolayer model could not sustain the characteristics of Ps, it was considered as an inefficient, unreliable and inaccessible model. Therefore, the 2 commonly used cell lines (NHEK) normal human epidermal keratinocytes and (HaCaT) immortalized human keratinocyte cell lines are used for the study of Ps. HaCaT cell lines is a very widely used method since it expresses several differentiation-gene products such as Keratin 1 and keratin 10 (KRT1 and KRT10) as well as gene markers such as filaggrin and involucrin. Apart from this it also expresses keratin usually found in primary keratinocyte culture i.e. keratin 7, keratin 8, keratin 18 and keratin 19. [38] Experimentation on the cell lines also has its disadvantages since it lacks blood vessels and leukocytes and does not entirely characterize a human psoriatic lesion. [1]

A few more new techniques have arrived such as a 3D engineered skin psoriatic cell model. De epimerized dermis and adult keratinocytes are used for characteristic features of Ps in vitro. [38]

In Silico Studies

Researchers have discovered drugs for psoriasis with the help of in silico screening methods such as genome-wide association studies (GWAS) and next-generation sequencing (NGS). But even before these methods came into use genetic research was done using family-based linkage studies. In a genetic analysis based on family linkage disequilibrium studies, 15 psoriasis susceptible regions (PSOR1-15) which are considered to be the main contributors in the disease pathogenesis were identified. The chromosome 6p21 located within the MHC (major histocompatibility complex) region has found out PSORS1 as the locus responsible for the development of the disease and it also accounts for the maximum heritability of the disease. PSORS1 is linked with the risk allele HLA-C which is associated with the disease pathogenesis as it is involved in handing over the antigens to CD8+ T-cells while traveling into the epidermis. On chromosome 17q25, PSORS2 was located and it encodes for the CARD14 gene. This gene mechanizes by activating the nuclear factor kappa B pathway, which mediates cell activation and proliferation. Mutations in the CARD14 gene can cause an inflammatory response and lead to psoriasis-like characteristics. PSORS3 was located on chromosome 4q near genes D4S1535 and IRF4 which are identified as the risk alleles for the disease pathogenesis. PSORS4 was located on 1q21 and was found to consist of epidermal differentiation complex (EDC). PSORS5 was found 3q21 by genome-wide studies. SLC12A8 gene was identified to be associated with Psoriasis Vulgaris and another gene CSTA (cystatin A) was found to be closely associated with keratinocyte differentiation in PSORS5 region. PSORS6 was found to be located on chromosome 19p13 and the risk factor is associated to type I psoriasis. It was found that linkage studies also have limitations since it cannot be used

for the study of complex diseases. [39] After the intervention of GWAS (genome-wide association studies) this problem was resolved since this type of research digs deep into problems such as alterations in the gene expressions in people affected with psoriasis. Our genetic makeup consists of various transcription factors (TFs) which play a role in the activation of immune cells, keratinocyte proliferation and differentiation in psoriasis. Studies have shown that when a drug is given, it directly targets the TFs and inhibits its action locally. [40]

GWAS is an array-based technique which is based on the mechanism of single nucleotide polymorphisms (SNPs). A case-control study is performed in a large meta- cohort of psoriatic and non-psoriatic patients. The main goal of this study is to find out the differentially expressed genes (DEGs) in psoriatic patients. These DEGs are screened to identify psoriasis responsive elements (PREs) using the library of binding sites. It was found out that only a fraction of DEGs encodes proteins that recognize PREs in the coding sites but when dODNs (double-stranded decoy oligonucleotides) are incorporated, it codes for PREs in the non-coding sites. dODNs are cis-elements targeted towards TFs which mimics as its DNA recognition site and inhibit its cellular activity. ETS1, IRF4, KLF4, RUNX3, STAT3, STAT5A and STAT5B are variants found near TF-encoding genes whose levels are found to be high in psoriasis patients which were found out by Genome-wide association studies (GWAS). Researchers have also used STAT3 dODN to treat lesions in psoriasis mouse models. This method has an advantage because it identifies DNA elements associated with the disease. [40] It also has certain drawbacks as it cannot be used to sequence an entire genome. A much more advanced technique then came into use called NGS (next-generation sequencing) which overcomes all the limitations by establishing targeted sequencing as well as whole genome sequencing. In a study conducted by Tang et al., exome sequencing was carried out to detect nonsynonymous single-nucleotide variants (SNVs) across the genome in a Chinese population and two low-frequency missense SNVs in genes IL23R and GJB2 were discovered which increased risk of Psoriasis. Since linkage studies and GWAS low frequency and rare variations are difficult to discover, NGS plays an important role in overcoming such limitations. [41] Yet another in silico screening analysis can be done using docking simulations. Mishra et al conducted an experiment based on the study of HSP (heat shock proteins) which are found to be overexpressed during Psoriasis and HSP70 are the one most widely expressed. Overexpression occurs when the skin is exposed to any kind of microbial agent in an unfavorable environment and stressful conditions. The immunoreactivity intensity distribution index (IRIDI) scores for HSP70 were substantially higher in the psoriatic patients than the normal human being when observed through skin biopsies. To constraint, the overexpression of HSPs docking analysis was carried out and 3D crystal structure of human HSP70 protein (PDB ID: 3JXU) was taken as the target protein in order to decrease the pathogenicity of the disease. The ligands were obtained from the natural product databases and anti-tumor ligand bases since they mostly do not have side effects. After protein and ligand preparation and optimization, the docking of each molecule was performed into the binding site of the target. The inhibitors for the HSPs were screened out based on their binding affinity with the target molecule. Schrodinger software (QikProp v3.3) was used to calculate the ADME properties of the ligands. Based on docking and glide scores 6 best hits

were identified from among 25000 compounds in the ligand libraries and among them, it was further observed that the resultant ligand 1,4-dinitrotetrahydroimidazo[4,5-d] imidazole-2,5(1H,3H)- dione can be considered one of the effective suppressors for psoriasis therapy.[42]

Herbal Medicines Used To Treat Psoriasis

Researchers found out that pharmacological therapy such as topical agents, phototherapy and systemic therapy lead to many side effects hence, they came up with herbal medicines as alternatives for the treatment of psoriasis. Following are the drugs which were found to have antipsoriatic activity.

PLANT	EXPERIMENT	TEST ORGANISM	OBSERVATION	REFERENCE
Aloe vera	Comparative study between topical Aloe vera (AV) and 0.1% triamcinolone acetonide (TA) cream	80 patients with psoriasis	Mean PASI score reduced from 11.6 to 3.9 (-7.7) with AV and 10.9 to 4.3 (-6.6) with TA Mean DLQI score reduced from 8.6 to 2.5 (-6.1) with AV and from 8.1 to 2.3 (-5.8) with TA cream	Choonhakam et al., 2009
	Therapeutic effectiveness of topical mixture of aloe vera and 1% coal tar (AMIX)	279 patients with mild to moderate psoriasis	PASI score reduced from 8.2±1.6 to 1.3±1.1	El gayyar et al., 2012
Andrographisnallamalayana	Therapeutic effectiveness of A. nallamalayana obtained from methanolic extract of whole plant	Imiquimod induced psoriasis in BALB/c mice	A. nallamalayana treated mouse showed reduction in levels of IL-22 (>59%) and Betamethasone treated mice showed reduction only by 47%	Parlapally et al., 2015
Wrightiatinctoria	Comparative study	Mouse tail	Degree of	Dhanabal

	of effectiveness between control, (Std.) isoretinoic acid (0.5mg/kg) and plant extract (200mg/kg)		orthokeratosis: control - 17.30 ± 4.09 standard - 57.43 ± 5.13 plant extract - 70.18 ±1.92 Drug activity was found to be highest in plant extract (63.94%) as compared to the standard (48.52%)	SP et al., 2011
Cassia tora	Antipsoriatic effect of ethanolic extract of C.tora leaves and flavonoids	UV-B induced rat photodermatitis model	Significant reduction in total epidermal thickness, significant retention of the stratum granulosum, absence of movement of neutrophils	Vijaylakshmi et al., 2014
	Screening of flavonoids of C. tora leaves using in silico docking simulations		Compounds luteolin-7-O-beta-glucopyranoside, quercetin-3-O-beta-D-glucuronide and gluco-aurantioobtusinbound more strongly to all the 15 studied antipsoriatic targets, except IL-	Akachukwu et al., 2018

			23	
Musa mysore (Poovan banana)	MTT assay was performed to check anti psoriatic activity using the ethyl extract of Poovan banana peel	HaCat cell lines	Extract reduces cell viability of selected psoriatic cell lines and inhibits proliferation of the cell lines significantly	Durga.E et al., 2013
Kigeliaafricana (sausage tree)	Determination of antipsoriatic property of methanol and hexane extracts of the stem, bark, leaves and fruit of *Kigeliaafricana*(sausage tree)	Male albino mice (Mouse tail method)	All the extracts showed activity in dose dependent manner wherein, K. africana stem (methanol and hexane extract) showed highest degree of % orthokeratosis as compared to K. africana leaves and fruit	Oyedegi et al., 2012
Smilax china	To assess anti-psoriatic activity of the methanol extract and isolated flavonoid quercetin from the rhizome of Smilax china (S. china) Linn.	Mouse tail method (Male albino mouse)	Quercetin induced notable degree of orthokeratosis in a dose dependent manner along with significant reduction in epidermal thickness was observed as compared to control. The methanol extract did not produce remarkable changes as compared to	Vijaylakshmi A et al., 2012

			retinoic acid and Quercetin	
Curcumin	Effect of curcumin in the inhibition of secretion of inflammatory factors	K14-VEGF transgenic mouse model	Reducedproduction of IL-17, IL-22, IFN-γ, IL-2, IL-8 and TNF-α in T-cells was noted. It was also observed that it inhibits the Kv13 K+ channel present on the T-cells.	Kang et al., 2016
Vitisvinifera	Activity of Vitisvinifera water extract in the inhibition of inflammatory conditions in human keratinocytes	HaCaT cell lines	It was found out that it can inhibit NF-κB pathway and reduces the expression of two typical markers of psoriasis i.e. IL-8 and VEGF.	Sangiovanni et al., 2019
Pine bark	Effect of Pine bark extract pycnogenol on IFNγ induced cell – cell adhesion and ICAM-1 expression	HaCaT cell lines	IFN-γ induced adhesion of T cells to keratinocytes is suppressed by PYC by inhibiting the expression of ICAM-1 on keratinocytes	Bito et al., 2000
Sugarcane (Saccharumofficinarum)	Effect of fatty acids extracted from sugarcane wax oil in reduction of epidermal differentiation	Mouse tail test	Study revealed that the extract from sugarcane induced higher % of orthokeratosis and drug activity in a dose dependent	Ledon et al., 2007

			manner	

Conclusion

This review summarizes various reports on herbal medicines used on different screening models to treat psoriasis. Traditionally medicinal plants have been in use for a long time to treat many different diseases and it has proven to be effective as an anti-psoriatic agent. Hence, this valuable information regarding different medicinal plants having the potential to treat psoriasis may be useful to scientists, doctors, and scholars working in the field of pharmacology and therapeutics to generate new drug formulations to cure Psoriasis and its types.

Conflict of Interest

The authors declare no potential conflict of interest

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