

Research Article

Update Aetiopathogenesis and Treatment of Psoriasis: A Literature Review

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Abstract

Background: Psoriasis is a very common skin condition that is caused by an immune system problem. T-cells, dendritic cells, macrophages and neutrophils all play a role in the proliferation of keratinocytes. Several genetic and environmental factors are involved in the development of this condition.

Objectives: The purpose of this study is to review aetiopathogenic causes and therapeutic aspects of psoriasis. Therefore, the literature review aims to address the following:

1. Explore psoriasis theories and factors that influence psoriasis.
2. Review of effectiveness of different treatment methods in the management of mild, moderate and severe psoriasis.
3. In addition, there is a need to identify and evaluate new or novel therapies in the treatment of moderate and severe forms of psoriasis.

Methods: A narrative literature review provides an overview of the extensive literature on the etiology, pathogenesis and treatment of psoriasis. The data comes from well reads articles published over the last 30 years (1992-2022). Electronic databases were taken from Google Scholar, PubMed, Medscape and the University of South Wales.

Results: Two hundred two articles, which varied between literature reviews, systematic reviews, review articles, randomized controlled studies, meta-analyses and comparative studies. 100 out of 202 of the articles in this thesis focused on discussing the etiology, pathogenesis, pathophysiology and psoriasis treatments.

Conclusion: Psoriasis is a multifactorial chronic disease. Genetics, immune and environmental factors play a significant role in its development. Psoriasis is a treatable but incurable disease that is widespread and has a significant impact on quality of life. Advances in understanding the

etiology and pathogenesis of psoriasis will undoubtedly lead to the discovery of new treatments and better patient outcomes and improve quality of life for patients.

Keywords: Psoriasis; Etiology; Pathogenesis; Pathophysiology; Treatment

Introduction

Psoriasis is a chronic, relapsing, inflammatory skin disease mediated by the immune system and it is characterized by keratinocytes proliferation and infiltration of T-cells, neutrophils, dendritic cells and macrophages [1]. Several genetic and environmental factors are involved in the development of this condition [2]. As a result, these environmental and genetic stimuli play a role in the pathogenesis of psoriasis [3]. It is possible to observe the etiology of psoriasis during its early stages, caused by trauma, infection, or medication, as well as during its maintenance phase in the chronic clinical course [4].

For the past 20 years, psoriasis has been considered an immune cell-driven disease and keratinocytes are the only observers of immune cell function in psoriasis [5]. Many regulatory factors can modulate keratinocytes; these factors are not independent but work together to alter the biological behavior of keratinocytes [6]. A study by Kimmell and Lebwohl, describe the process of psoriasis, which is characterized by the development of red, erythematous plaques with definite borders and scale-covered surfaces. Psoriasis comes in a variety of forms, such as pustular, guttate, palmar-plantar and erythroderma [7]. More than 80% of patients with psoriasis have the plaque type [8]. Before choosing a course of treatment, it is essential to understand the etiopathogenesis of psoriasis and the extent and clinical severity of skin lesions [9].

Conventional treatment of psoriasis ranges from topical therapy (emollients, topical corticosteroids, vitamin D analogues to systemic therapy. Topical treatment is the mainstay of treatment for mild to moderate psoriasis with limited side effects. Systemic treatments alone or in a combination with UVA/UVB phototherapy are used in cases of moderate to severe psoriasis or in cases that do not respond to topical treatment [10].

As part of the "Psoriasis Area and Severity Index", the area of severity index is determined by erythema, thickness and degree of desquamation (scale) of lesions on the head, arm, trunk and legs ("Fig. 1 below shows the PASI score") [11]. Houghton, et al., investigated the correlation between the PASI score and Dermatology Life Quality Index (DLQI) domain score in selected patients with moderate to severe psoriasis and severe psoriatic (PsA) comorbidities [12]. Houghton and colleagues; conclude that patients who show improvement in skin symptoms may have an improvement in Quality of Life (QoL).

Methodology

The data comes from well reads articles published over the last 30 years (1992-2022). A literature search was conducted using, electronic databases were taken from Google Scholar, PubMed, Medscape and the University of South Wales Library. The following search terms were used: "psoriasis" and "etiology", "histopathology", "pathogenesis" "cutaneous immunity", "T- cells", "tissue memory residentT-cells", "cytokine", "pathophysiology", "medication, therapy".

Many articles are discussed to explore the latest research on the etiology, pathogenesis and pathophysiology of psoriasis. In particular, articles on the treatment of mild, moderate and severe psoriasis are reviewed. The search is conducted only for the most relevant and reliable published works of literature and articles and was limited to articles written in the English language. To filter the results based on the inclusion and exclusion criteria, the abstracts and, when necessary, the full texts of all the obtained literature were examined.

Inclusion criteria

1. Articles between (1992-2022) are included
2. Title and abstract of these literature reviews have been checked for consistency and duplicate have been removed
3. Articles were written in the English language
4. Articles related to the purpose of this literature review and the scope of the search are included

Exclusion criteria

1. Articles before or prior to 1992 are excluded
2. Duplicate articles and abstracts are removed
3. Articles written in other languages are excluded
4. Articles deemed unrelated to the purpose of this literature review or beyond the scope of the search are excluded

Epidemiology

Psoriasis affects approximately 60 million people worldwide. This is more common in high-income areas and places with an aging population [13]. According to Keegan and Bagal, 1-3% of people worldwide have psoriasis [14]. Although psoriasis can manifest at any age, it is traditionally believed to have a bimodal distribution, peaking at ages 30 to 40 and then again at 50 to 60 [15]. Based on the bimodal distribution age of onset and hereditary, two types of psoriasis have been discussed.

Type I psoriasis "accounts for approximately 65% of the population with psoriasis and is associated with onset before age 40" and type II psoriasis "accounting the remainder of the population with psoriasis" [16]. Early-onset disease or type I psoriasis patients frequently have more relatives who are afflicted by psoriasis than patients with late-onset disease or type II psoriasis [17].

Aetiology and Risk Factors of Psoriasis

Psoriasis is a multifactorial condition that is significantly influenced by both endogenous and exogenous factors [1]. A genetic predisposition is considered an important factor, especially in people with early onset of the disease (before age 40 years) [18]. In previous studies from 1982 to 2000, the factors that caused Japan's population to exacerbate psoriasis were psychogenic (stress) (6.4% to 16.6%), seasonal factors (9.7% to 13.3%), infection (3.5% to 8.3%), exposure to radiation of sunlight (1.3% to 3.5%) and drugs (0.9% to 2.3%). Associated diseases include hypertension (1.1-27.8%) and Diabetes Mellitus (DM) (7.0 - 13.9%) [19-21]. Weiss, et al., found that the Koebner phenomenon is well-known to occur at the site of trauma [22]. Patients with psoriasis have a significantly higher prevalence of obesity [23]. These etiology and Risk factors of psoriasis are summarized and illustrated in Table 1.

Etiology and Risk factors	Comment	Reference
Genetic factors	The incidence in monozygotic twins is higher than in dizygotic twins. According to a literature review, "of 141 monozygotic twins pairs, 82 had psoriasis and 59 did not; of 155 dizygotic twins pairs, only 31 had psoriasis and 124 did not".	[38], [39]
Trauma	Studies show Koebner phenomenon is well known to occur at the site of trauma. A few of the various mechanisms that aid in the growth of new psoriatic lesions include tryptase, IL-6, IL-8, IL-17 and IL-36. Furthermore, Koebnerization is promoted by elevated Vascular Endothelial Growth Factor (VEGF) levels.	[22],[40],[41]
Infections	Infection with streptococcus pyogenes, Staphylococcus aureus, Candida species and Human Immunodeficiency Virus (HIV).	[42],[43],[44],[45]
Drugs	Studies show that drugs causing psoriasis flare-ups by medication include: lithium, beta-blockers, nonsteroidal anti-inflammatory drugs, antimalarial and tetracycline. Psoriasis can also be caused by biological agents that are recognized as paradoxical reactions.	[46], [47]
Sunlight	This study explains that strong sunlight can cause psoriasis flare-up, which is worse in the summer on exposed skin, even though sunlight is beneficial for a small percentage of patients.	[48]
Pregnancy	Pregnancy was initially recognized as a Th2 phenomenon, but recent studies have shown it to increase during pregnancies. Several cytokines and cytokine-modulating molecules may have anti-inflammatory effects in Th-1 dominant disease. In addition, successful pregnancy is associated with regulatory T-cell activity and reduced Th17.	[49], [50]
Psychogenic	A previous systematic review of 39 studies (32,537 patients), 46% of patients believed that their illness was a response to stress and 54% remembered previous stressful events	[51]
Cigarette	A study found that the amount and/or duration of smoking were positively associated with the incidence of psoriasis.	[52]
Alcohol	A study by Svanström and colleagues, demonstrated that increased alcohol intake may trigger and worsen psoriasis by increased tumor necrosis factor- α (TNF- α) production from peripheral blood monocytes and macrophages, as well as the proliferation and activation of lymphocytes	[53]
Obesity	A study demonstrated that patients with psoriasis have a significantly higher prevalence of obesity as well as a higher risk of obesity.	[23]
Hypertension	In a hypertensive meta-analysis, patients with psoriasis had a higher prevalence and incidence of hypertension.	[54]
Diabetes Mellitus	According to these studies, patients with psoriasis are more likely to develop type I diabetes. Type II diabetes does not directly contribute to the pathogenesis of psoriasis.	[55], [56]

Table 1: Summary of etiology and risk factors of psoriasis.

Pathogenesis

One characteristic of psoriasis is persistent inflammation, which leads to uncontrolled keratinocyte proliferation and decreased differentiation [3,4]. The pathogenesis of psoriasis can be seen in the early stages, which can be caused by trauma (Koebner's phenomenon), infection, or drugs and in the maintenance stages, which are characterized by a chronic clinical course [4].

A study conducted by Ni and Lai, appeared that the pathogenesis of psoriasis is complex and involves the interaction between keratinocytes, immune cells and other skin cells [5]. Over the past two decades, psoriasis has been seen as a disease driven by immune cells so they believed keratinocytes are the only performers of immune cell function during psoriasis.

Other studies explain that the IL-23/IL-17 virulence axis is the key to driving psoriasis. Plasmacytoid cell activation of IL-12, IL-23 and TNF- α leads to activation of Th1 and Th17, which in turn induces inflammatory responses such as IL-17, IL-21 and IL-22. These cytokines (particularly IL-17) then activate keratinocytes, causing them to produce cytokines, chemokines and antimicrobial peptides that help increase inflammation [3,24,25].

A study by Lai and Gallo, found that Antimicrobial Peptides (AMPs), Dendritic Cells (DCs), Tumor Necrosis Factor (TNF), IL-23, Th17, IL-17, IL-22, Signal Transducers and Activators of Transcription (STAT-3) and Tissue Resident Mnemonics (TRMs) contribute significantly to its pathogenesis [26].

Keratinocytes are involved in the early and maintenance stage of psoriasis so several factors that can modulate keratinocytes, including genetic regulation, cytokines and receptors, metabolism, cell signaling, transcription factors, non-coding RNAs, antimicrobial peptides and other proteins with various functions. These regulators are not independent but work together to alter the biological behavior of keratinocytes through several mechanisms that link them to psoriasis [6]. The pathogenesis of disease involves an interaction between two groups of immune cells and their corresponding signaling molecules [27].

1. The effects of innate immune cells such as neutrophils, Langerhans cells and Natural Killer T-lymphocytes (NK) are mediated by Antigen-Presenting Cells (APCs).
2. Adaptive or acquired immune cells that are obtained through mature skin CD4+ and CD8+ T lymphocytes [28].

A study by Gaspari, showed that the innate immune response occurs minutes to hours after exposure to an antigen, but memory does not develop when the antigen is reactivated [29]. However, the adaptive immune response takes days to weeks to respond to an antigen challenge. Adaptive immune cells have the ability to respond to a large number of antigens and develop immunological memory by remodeling antigen receptors on B and T-cells. The pathogenesis is summarized and illustrated in Table 2.

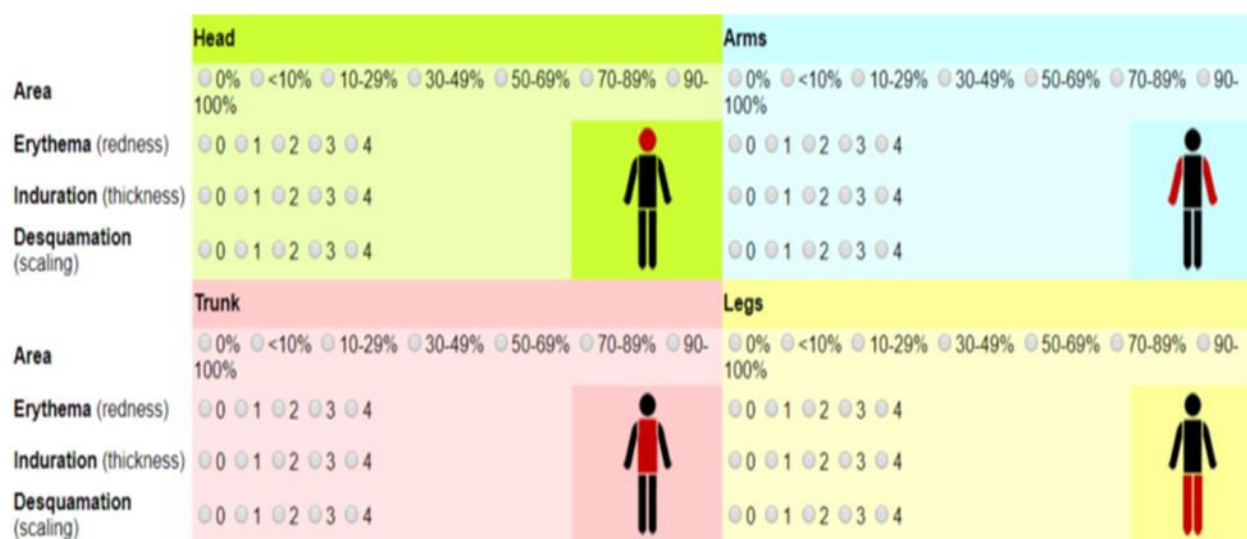


Figure 1: The PASI calculator is easily found online Corti M (2019).

Pathogenesis	Comment	Reference
Keratinocyte	These studies explain that the pathogenesis of psoriasis is complex and involves the interaction between keratinocytes, immune cells and other skin cells.	[5] [6]
Plasmacytoid cell activation	A study demonstrated that plasmacytoid cell activation of TNF- α , IL-12 and IL-23 leads to activation of Th1 and Th17.	[3]
Antimicrobial peptides (AMPs)	A study found that the Antimicrobial Peptides (AMPs), Dendritic Cells (DCs), tumor necrosis factor (TNF), IL-23, Th17, IL-17, IL-22, Signal Transducers and Activators of Transcription (STAT-3) and Tissue Resident Mnemonics (TRMs) contribute significantly to its pathogenesis.	[26]
IL-17	Cause keratinocytes activation.	[24]
IL-23	Cause keratinocytes activation to produce antimicrobial peptides, cytokines and chemokines that help increase inflammation.	[25]
Innate immune cells	This study showed that innate immune cells are mediated by antigen-presenting cells (APCs) ("including natural killer T lymphocytes (NK), Langerhans cells and neutrophils").	[27]
Acquired or adaptive immune cells	These studies showed that adaptive immune cells mediated by "mature skin CD4+ and CD8+ T lymphocytes".	[28], [29]

Table 2: Summary of pathogenesis of psoriasis.

Pathophysiology

Interactions between T-cells and keratinocytes are a hallmark of the immune-mediated pathophysiology of psoriasis. Several cytokines have been shown to play important roles, including TNF-alpha, IL-1, 8 and 23, intercellular adhesion molecule 1 and e-selectin [3]. There are three main stages of psoriasis pathophysiology: (1) Epidermal proliferation (2) Angiogenesis (3) Accumulation of inflammatory cells. The Pathophysiology is summarized and illustrated in Table 3.

T-cells	Studies demonstrated that the epidermis is infiltrated by a number of activated T-cells capable of inducing keratinocyte proliferation.	[57], [58]
Angiogenesis	Studies showed that vertical dermal capillary loops expand, stretch and twist. It is increased more than 4 times by angiogenesis due to endothelial proliferation of microvessels in the upper dermis, or by secreting angiogenic mediators like Vascular Endothelial Growth Factor (VEGF), Tumor Necrosis Factor (TNF), interleukin-8 (IL-8), epidermal keratinocytes are a major contributor to angiogenic activity, as well as basic Fibroblast Growth Factor (bFGF). The degradation of the ECM also leads to the release of pro-angiogenic factors (VEGF, bFGF, IGF-1 (insulin-like growth factor)) stored in the ECM that promote angiogenesis.	[59],[60],[61],[62],[63],[64],[65]
VEGF (Vascular Endothelial Growth Factor)	This study found that angiogenic mediators contribute to angiogenic activity.	[66]
bFGF (basic fibroblast growth factor)	These studies demonstrated that the angiogenic mediators with VEGF cause Extracellular Matrix (ECM) rupture in the later stages of angiogenesis, which also include vasodilation, increased vascular permeability, destabilization of preexisting blood vessels and proliferation and migration of Endothelial Cells (ECs).	[67] [66]
E-selectin	Cause up-regulation of Intercellular Adhesion Molecule-1 (ICAM-1) on dermal vessels in affected tissues.	[68]
Histamine,	A study demonstrated that these inflammatory mediators in skin	[69]

neuropeptides	capillaries actively contribute to the inflammatory process by surface expression of molecules involved in leukocyte localization.	
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Table 3: Summary of pathophysiology of psoriasis.

Drug	Mechanism of Actions	Adverse Effects	Reference
Vitamin D Analogues (Tacalcitol, Calcipotriol,Maxacalcitol)	Interferes with genes, causing epidermal keratinocytes to differentiate and proliferate more slowly. Anti-inflammatory effects can occur by inhibiting the production of IL-2, IL-6 and interferon-gamma (IFN- γ).	Irritation of the skin. Generally, well tolerated. Irritation of the skin. Erythem, pruritus, irritation and itching.	[70],[71],[72],[73],[74],[75],[76]
Corticosteroids	Inhibits the generation of pro-inflammatory cytokines through the regulation of gene transcription, leading to decreased IL-1 Synthesis.	Skin atrophy and suppression of the adrenal axis are side effects of long-term treatment	[77], [78]
Dithranol	Causes mitochondrial dysfunction, which results in the resumption of cell differentiation and a reduction in keratinocyte proliferation.	Having the potential to irritate the skin and leave stains on the skin.	[79], [80]
Tacrolimus	Inhibition of both calcineurin phosphatase activity and inflammatory mediator production.	Well tolerated, cause minor irritation of the skin	[81], [82]
Retinoid	Can modify gene transcription by specifically adhering to β and retinoic acid that are present in keratinocytes cell membranes.	Erythem, burning, stinging and scaling.	[83], [84]
Keratolytic Agents	Acts by desquamating corneocytes.	Irritation of the skin and burning sensation	[85], [32]

Table 4: Summary of topical agents for the treatment of psoriasis.

Drug	Mechanism of Action	Adverse Effect	Reference
Methotrexate	An anti-folic acid agent that blocks the synthesis of purines, inhibits dihydrofolate reductase and induces lymphatic programmed cell death.	Gastrointestinal problems such as erosion of the oral mucosa, diarrhea, bleeding, ulcer, bone marrow suppression	[86],[87]
Cyclosporine	Reducing IL-2 by inhibiting calcineurin.	Hypertension, gingival hyperplasia, hirsutism, renal impairment, severe infection	[88],[89]
Acitretin	Binding to the retinoid receptor so cause the normalization of keratinocyte proliferation and differentiation.	Dry lips, stomatitis, night vision, teratogenicity	[90]
Fumarate	The mechanism of action appears to be immune regulation, leading to apoptosis of activated T-cells and	Flushing, nausea, vomiting and heartburn	[91]

	changes in cytokine secretion. Th2 response is promoted by intracellular glutathione, which also modulates Nrf2, NF- κ B and HIF-1 α .		
Apremilast	Inhibits phosphodiesterase-4 (PDE4). As a result, both immune and non-immune cells have higher intracellular cAMP levels, which reduce inflammation.	Headache, nausea and vomiting	[92],[93]
Etanercept	Constituted the first TNF- α inhibitor. Human fusion protein dimer that mimics TNF- α R.	Weakness, nausea, sore throat or burning, redness or itching and pain or swelling at the injection site	[94],[32]
Infliximab	It works by blocking TNF- α or TNF- α receptors.	Increased risk of infection and malignancy	[95]
Adalimumab	Human monoclonal antibody against TNF- α .	Active infection	[96]
Certolizumab pegol	The Fab protein of human monoclonal antibody against TNF- α conjugated to polyethylene glycol.	Serious infections, lymphomas, or other malignancies.	[97],[33]
Ustekinumab	Targets IL-23 and IL-12 by neutralizing IL-23. human IgG1K monoclonal antibody that binds specifically to the p40 protein subunit.	Sore throat, joint pain, headache, nausea	[98],[99]
Tildrakizumab	Human-compatible IgG1k selectively blocks IL-23 by attaching to its P19 subunit.	Cardiovascular events, infections (serious or severe infections), dizziness, sore throat, joint pain, headache, nausea and pain at the injection site.	[100],[101],[102]
Guselkumab	The IgG1 λ monoclonal antibody against IL-23 by attaching to its p19 subunit.	Dizziness, sore throat, joint pain, headache, nausea.	[103],[104],[105]
Risankizumab	Humanized monoclonal IgG1 antibody that blocks the p19 subunit of IL-23.	Upper respiratory tract infection, viral urinary tract infections	[106],[107],[108]
Secukinumab	Anti-IL-17 human monoclonal IgG1k antibody.	Risk of infection	[109],[110]
Ixekizumab	Humanized monoclonal antibody directed to IL-17RA.	Diarrhea, upper respiratory tract infections, sinusitis, oral herpes and conjunctivitis	[111],[112],[113]
Brodalumab	IgG2 monoclonal antibody directed to IL-17RA.	Upper respiratory tract infection, sinus conjunctivitis, nasal congestion	[114],[115],[116]
Baricitinib	JAK1 and JAK2 inhibitors.	Cytopenia, anemia	[117]
Peficitinib	Pan JAK inhibitor with JAK3 selectivity.	Without significant side effects in a Phase IIa study	[118]
Ruxolitinib	JAK1 and JAK2 inhibitors.	Muscle and joint pain	[119]
Tofacitinib	JAK1/3 inhibitor.	Cytopenia and infections	[37]
Phototherapy (NBUVB) and (PUVA)	Biological mechanisms by which phototherapy therapy improves psoriasis are: 1) changes in cytokine	Cause skin irritation and erythema. PUVA has photocarcinogenicity. Should be avoided during pregnancy	[120]

	profile, 2) induction of apoptosis, 3) increased immunosuppression.	and lactation.	
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Table 5: Summary of systemic treatments for psoriasis.

Treatment

As with other complex immune-mediated diseases, there is no definitive cure for psoriasis and the only treatment available is to reduce disease activity and improve symptoms. Therapies are administered according to disease severity and assessed by the Psoriasis Area and Severity Index (PASI, ranging from 0 to 72), which takes into account the appearance and extent of lesions [30]. Conventional therapies range from topical treatments (emollients, topical corticosteroids, vitamin D analogs) to systemic treatments.

Topical treatment is the mainstay treatment with limited adverse effects used for mild to moderate psoriasis. In severe cases of psoriasis or cases that fail to respond to topical treatment, used systemic treatments (UVA/UVB phototherapy or systemic therapies are reserved for moderate-to-severe cases [10]. The primary goal of psoriasis treatment is to reduce the symptoms and all visible manifestations of the lesion [31].

Topical Treatment

It serves as the mainstay of treatment for mild to moderate psoriasis. However, in severe cases, the use of systemic therapy in addition to topical therapy may be beneficial [32].

Systemic Therapies

The use of systemic therapy for moderate to severe psoriasis is recommended when the PASI or Dermatology Life Quality Index (DLQI) > 10, when all other treatments have failed, or when alternative treatments are contraindicated because of allergy [33]. Systemic therapy is an evolving field and includes biological and non-biological agents. Biological agents, which are monoclonal antibodies, target specific parts of the immune system, unlike the broader mechanism of action of non-biological agents [34]. In more severe stages of psoriasis, biological drugs and phototherapy are recommended [35]. The treatments are summarized and illustrated in Table 4,5 [36,37,117-119].

Conclusion

Psoriasis is a chronic, multifactorial disease. Genetic, immunological and environmental factors play an important role in its development. Psoriasis is a treatable but incurable disease that is widespread and has a significant impact on quality of life. In order to understand the treatment of this disease, it is important to understand its etiology. Therefore, this review dealt with the various studies that contributed to the discovery of the etiology of psoriasis, pathogenesis, pathophysiology and treatment. It also mentioned the relationship between the causes of psoriasis and environmental and genetic factors on the one hand and how to treat psoriasis by knowing those causes, pathogenesis and pathophysiology on the other hand and this led to the repercussions of the development of treatment during its different stages of time, which led to the discovery of a novel biological treatments. Also, this review included all the studies that mentioned the adverse effect of both traditional medicines to treat psoriasis and the adverse effects of biological treatments. So, the literature review reported all availability of treatments for psoriasis that has been grown over the past few decades, making it easier for people with this disease to improve their quality of life. Topical medications are traditionally used to treat mild and moderate psoriasis like (corticosteroids, vitamin D3 and retinoids) and they are fewer adverse effects in comparison with systemic medication. The role of systemic medication is becoming more and more important. Cyclosporine, methotrexate and acitretin are systemic drugs approved for the treatment of moderate to severe psoriasis. In general, these three drugs are associated with organ toxicity, especially hepatotoxicity for methotrexate, high blood pressure and renal toxicity for cyclosporine, as well as teratogenicity for acitretin. Therefore, a specific systemic of T-lymphocytes is necessary. Biological drugs are the type of treatment that has been at the forefront of clinical research over the past 10 years, promising to improve the disease remission rate and reduce the long-term risks associated with it. Organs such as (the liver, kidneys, bone marrow, etc.) exposed to these novel biological agents do not appear to be persistently toxic and side effects are increased with mild flu-like symptoms and infections (e.g., herpes simplex), or slightly equivalent to a placebo. Therefore, there

are newer therapies such as apremilast, which inhibits Phosphodiesterase-4 (PDE-4) and tofacitinib, baricitinib, peficitinib, ruxolitinib which are a Janus Kinase Inhibitor (JAK inhibitor). Many of these novel therapies have become available to treat and improve severe types of psoriasis.

Conflict of Interest

Dr. Hsuan-Hsiang Chen, the Editor-In-Chief at the Journal of Dermatology Research, had a role in the peer review process and the decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

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