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Review Article

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The Pathophysiological Insights and Emerging Biomarkers in Psoriasis: A Comprehensive Review

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Abstract

Psoriasis is a chronic, immune-mediated inflammatory skin disorder affecting 2-3% of the global population. It imposes a substantial burden on patients due to its relapsing nature, lifelong management, and association with systemic comorbidities, including psoriatic arthritis, cardiovascular diseases, and metabolic syndrome. The unpredictable disease course and heterogeneity in treatment response necessitate the identification of reliable biomarkers to enhance clinical decision-making. Biomarkers hold promise in refining diagnosis, assessing disease severity, predicting treatment outcomes, and enabling precision dermatology in psoriasis management. Recent advancements in multiomics research have led to the discovery of potential psoriasis biomarkers, including genetic markers (*HLA-C** 06:02), inflammatory cytokines (IL-17, IL-23, TNF-α), proteomic and metabolomic signatures, and skin microbiome alterations. These biomarkers correlate with disease activity, therapy responsiveness, and risk of comorbid conditions, thereby facilitating personalized treatment approaches. Despite promising findings, their routine clinical application remains limited due to variability in study methodologies, lack of standardization, and insufficient large-scale validation. The future of biomarker-driven dermatology in psoriasis depends on the integration of molecular profiling, standardized validation protocols, and clinical trials to establish their predictive and prognostic utility. Regulatory approval and widespread clinical adoption require rigorous validation and harmonization of biomarker assessment techniques. Establishing a clinically reliable biomarker panel could revolutionize psoriasis management by enabling targeted therapies, optimizing treatment efficacy, and minimizing adverse effects. This review aims to provide a comprehensive analysis of the current landscape of psoriasis biomarkers, their clinical relevance, and future directions for their standardization and integration into precision dermatology.

Keywords: Clinical relevance, Dermatology, Genetic markers, Interleukin-17, Proteomics, Psoriasis

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Introduction

Psoriasis is a persistent inflammatory dermatologic disorder, impacting approximately 2–3% of the global population (1-3). Clinically, it manifests as erythematous, scaly plaques, primarily resulting from accelerated keratinocyte proliferation and immune system activation. Although traditionally considered a skin condition, psoriasis is now recognized for its systemic implications, as it is commonly associated with psoriatic arthritis, cardiovascular disease, metabolic syndrome, and mental health disorders (4,5) (Table 1). These comorbidities elevate the burden of the disease, complicating patient management, and often necessitating lifelong therapeutic interventions (6). The underlying pathogenesis of psoriasis is multifactorial, involving a dynamic interaction between genetic predispositions, immune system dysregulation, and environmental triggers. Central to the inflammatory process are immune cells, particularly T-helper 17 (Th17) cells, and cytokines such as IL-17, IL-23, and TNF-α (7,8). These mediators promote an inflammatory cascade that drives both the local skin lesions and the systemic effects of the disease. Genetic factors, such as the *HLA*-C06:02 allele, have been identified as the key contributors to psoriasis susceptibility, while immune-mediated pathways are responsible for the disease's chronic nature and variability in clinical expression and response to treatment (9,10). This complexity necessitates the identification of accurate biomarkers to assist in diagnosis, monitor disease progression, predict therapeutic responses, and enable more personalized treatment plans. Emerging biomarkers in psoriasis research span a wide spectrum, including genetic markers, inflammatory mediators, proteomic and metabolomic signatures, and shifts in the skin microbiome (11,12). Notably, the *HLA*-C06:02 allele and cytokines like IL-17, IL-23, and TNF-α correlate with disease severity and treatment outcomes. Advances in proteomics and metabolomics have also uncovered potential circulating biomarkers that may serve as indicators of disease activity or therapeutic efficacy (13). However, the clinical integration of these biomarkers remains limited by

Table 1. Clinical manifestations of psoriasis

Clinical manifestation	Clinical findings
Plaque psoriasis	This type is characterized by sharply defined erythematous plaques, usually more than 0.5 *cm* in diameter, often covered with silvery scales. It can present as isolated lesions or as a generalized form.
Scalp psoriasis	One of the most commonly affected areas, scalp psoriasis often features thick scaling and inflammation, making it particularly difficult to treat.
Palmoplantar psoriasis	Affects the palms of the hands and soles of the feet, presenting with varying degrees of redness and scaling, from poorly defined fissured areas to large plaques.
Flexural psoriasis	Also known as intertriginous or inverse psoriasis, it presents with thin, minimally scaly plaques in skin folds like the axillary, groin, genital, and inframammary regions.
Nail psoriasis	Nail involvement may occur without visible skin lesions and is marked by pitting, subungual hyperkeratosis, oil drop sign, distal onycholysis, and splinter haemorrhages. Nail psoriasis is a strong indicator for psoriatic arthritis.
Guttate psoriasis	Typically appearing as small, salmon-pink, scaly papules resembling "dew drops" on the trunk or limbs, often following an episode of group A streptococcal throat infection or perianal dermatitis.
Pustular psoriasis	Characterized by clusters of sterile pustules on inflamed, red skin, commonly concentrated on the palms or soles, often painful.
Erythrodermic psoriasis	A severe, life-threatening form of psoriasis involving widespread erythema covering more than 90% of the body, often with minimal scaling. It may result in complications such as hypothermia, electrolyte imbalances, and heart failure.
Annular psoriasis	Presents as well-demarcated, erythematous plaques with central clearing, forming a ring-shaped appearance on the skin.

factors such as inter-patient variability, inconsistent research methodologies, and a lack of standardized validation across diverse populations. Overcoming these challenges and integrating multiomics data with rigorous clinical validation holds the potential to significantly advance psoriasis management. The successful incorporation of biomarkers into clinical practice could ultimately enable more targeted therapies, improve treatment response, and reduce side effects, ushering in an era of precision dermatology (14-16).

Pathophysiology of psoriasis

Psoriasis is a chronic, immune-mediated inflammatory skin disorder characterized by abnormal keratinocyte proliferation, impaired differentiation, and persistent immune activation. The disease results from a complex interaction between genetic predisposition, environmental factors, and immune system dysregulation, leading to epidermal hyperplasia and chronic inflammation. The key driver of psoriasis pathophysiology is an overactive immune response involving innate and adaptive immune mechanisms, where dendritic cells, T cells, neutrophils, and keratinocytes engage in a self-sustaining inflammatory cycle. The IL-23/IL-17 axis has emerged as the primary pathway responsible for disease chronicity, orchestrating the inflammatory cascade that leads to psoriatic plaque formation and systemic involvement (6,-7,17). The summary of psoriasis pathophysiology is shown in table 2.

Table 2. Summary of psoriasis pathophysiology

Key aspects	Pathophysiological mechanism
Immune dysregulation	Psoriasis is driven by an overactive immune response, involving excessive activation of innate (plasmacytoid dendritic cells, myeloid dendritic cells, neutrophils) and adaptive (Th1, Th17, Tregs) immune pathways, leading to chronic inflammation
IL-23/IL-17 Axis	IL-23, secreted by myeloid dendritic cells, promotes Th17 differentiation. Th17 cells release IL-17A, IL-17F, and IL-22, which stimulate keratinocyte hyperproliferation, chronic inflammation, and epidermal thickening
Keratinocyte dysfunction	IL-17A and IL-22 cause excessive keratinocyte proliferation, impaired differentiation, and increased production of antimicrobial peptides (AMPs), leading to epidermal barrier disruption and persistent immune activation
Antimicrobial peptides (AMPs)	LL37 (cathelicidin), β-defensins, and S100 proteins are overexpressed in psoriatic skin. They form complexes with self-DNA and self-RNA, triggering plasmacytoid dendritic cell activation, leading to IFN-α production and sustained immune stimulation
Cytokine cascade	A self-sustaining inflammatory loop is created by IL-17, IL-23, TNF-α, IFN-γ, and IL-22, which recruit and activate immune cells, maintaining the chronic nature of psoriasis
Angiogenesis & vascular changes	Increased Vascular Endothelial Growth Factor (VEGF) expression promotes angiogenesis, capillary dilation, and endothelial dysfunction, enhancing immune cell infiltration into psoriatic plaques
Genetic susceptibility	Psoriasis has a strong genetic component, with HLA-C*06:02 being the most significant risk factor. Other implicated genes, including IL23R, TNFAIP3, STAT3, TYK2, and LCE3B/C, contribute to immune dysregulation, epidermal barrier dysfunction, and inflammatory signalling
Environmental triggers	Infections, physical trauma (Koebner phenomenon), psychological stress, and medications (β-blockers, NSAIDs, lithium, antimalarials) can activate innate immune responses and worsen disease severity in genetically predisposed individuals
Chronic inflammation	Continuous IL-23/IL-17 axis activation, persistent keratinocyte dysfunction, and ongoing dendritic cell stimulation result in long-term epidermal hyperplasia, immune infiltration, and chronic plaque formation
Targeted therapy	Advances in biologic therapies (IL-17, IL-23, and TNF inhibitors) have revolutionized psoriasis treatment by interrupting inflammatory pathways, reducing immune activation, and improving disease control

Immune system dysregulation in psoriasis

Psoriasis is an immune-mediated condition where both innate and adaptive immune responses contribute to disease initiation and progression. The innate immune system plays a role in the early stages of disease by triggering an inflammatory response, while adaptive immunity sustains chronic inflammation (18).

Innate immune activation

The innate immune system is the first line of defence against external triggers, playing a critical role in initiating psoriatic inflammation. Plasmacytoid Dendritic Cells (pDCs) are abnormally activated in psoriatic skin, recognizing self-DNA and RNA complexes bound to antimicrobial peptides (AMPs) such as LL37 (cathelicidin). These immune complexes activate Toll-like receptors (TLR7 and TLR9) on pDCs, leading to the secretion of type I interferons (IFN-α and IFN-β), which, in turn, activate myeloid Dendritic Cells (mDCs). Once activated, mDCs secrete IL-12 and IL-23, which promote the differentiation of Th1 and Th17 cells, respectively (19-20).

Adaptive immune activation and the IL-23/IL-17 Axis

The IL-23/IL-17 axis plays a central role in sustaining psoriatic inflammation. IL-23, produced by dendritic cells and macrophages, promotes the expansion and survival of Th17 cells, which secrete IL-17A, IL-17F, and IL-22. IL-17A stimulates keratinocyte proliferation and enhances the release of inflammatory mediators, further attracting immune cells into psoriatic lesions. IL-22 contributes to epidermal thickening by promoting keratinocyte survival and abnormal differentiation (21-22). Additionally, TNF-α and IFN-γ further amplify inflammation, sustaining a chronic immune response. Normally, regulatory T cells (Tregs) counteract excessive immune activation, but in psoriasis, Treg function is impaired, allowing unchecked Th17-driven inflammation.

Keratinocyte dysfunction and epidermal hyperplasia

A hallmark of psoriasis is keratinocyte hyperproliferation and altered differentiation, leading to thickened, scaly plaques. Histopathologically, psoriatic skin exhibits acanthosis (epidermal thick-ening), parakeratosis (retention of nuclei in the stratum corneum), elongation of rete ridges, and loss of the granular layer. IL-17A and IL-22 stimulate keratinocytes to proliferate excessively, while simultaneously impairing differentiation, resulting in abnormal barrier function and enhanced immune activation. Additionally, keratinocytes themselves act as immune-active cells, producing cytokines such as IL-1, IL-6, and TNF-α, which recruit additional inflammatory cells, reinforcing chronic inflammation (23,24).

Role of antimicrobial peptides (AMPs) in psoriasis

AMPs play a dual role in immune defence and autoimmunity by both protecting against infections and contributing to chronic inflammation. In psoriasis, AMPs such as LL37, β-defensins, and S100 proteins are overexpressed, amplifying immune responses. LL37 forms immune-stimulatory complexes with self-DNA and self-RNA, triggering pDC activation *via* TLR7/9 and leading to the persistent production of IFN-α, which enhances Th17-driven inflammation. β-Defensins and S100 proteins act as chemoattractants, drawing more immune cells into psoriatic lesions and exacerbating the disease process. This self-sustaining cycle of AMP overexpression, immune activation, and keratinocyte dysfunction is a fundamental component of psoriasis pathophysiology (25-27).

Angiogenesis and vascular abnormalities in psoriasis

Psoriatic lesions exhibit increased angiogenesis and vascular remodelling, contributing to erythema, immune cell infiltration, and chronic inflammation. VEGF is highly upregulated in psoriatic skin, promoting neovascularization, capillary dilation, and endothelial dysfunction. This vascular remodelling facilitates the migration of immune cells into psoriatic plaques, reinforcing inflammation. Additionally, the dilated and inflamed blood vessels sustain immune cell trafficking, worsening disease progression (28, 29).

Genetic susceptibility and environmental triggers

Genetic predisposition plays a significant role in

the development of psoriasis. The strongest genetic association is with *HLA*-C*06:02, which is involved in antigen presentation and T-cell activation. Other implicated genes include IL23R, TNFAIP3, STAT3, TYK2, and LCE3B/C, which regulate cytokine signalling, NF-κB activation, and epidermal barrier function. Environmental factors such as infections, trauma (Koebner phenomenon), psychological stress, and medications [β-blockers, lithium, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), antimalarials] can act as triggers, exacerbating inflammation and inducing disease flares. These external stimuli activate innate immune responses, leading to dendritic cell activation, cytokine secretion, and immune cell recruitment, contributing to disease progression (26, 30).

The IL-23/IL-17 axis and chronic inflammation

The IL-23/IL-17 axis is the most critical inflammatory pathway in psoriasis, responsible for its chronicity. IL-23 secreted by dendritic cells maintains Th17 cell differentiation, leading to continuous IL-17A and IL-17F production. These cytokines stimulate keratinocytes to produce additional inflammatory mediators, perpetuating a self-amplifying inflammatory loop. IL-22 further drives epidermal hyperplasia, while TNF-α and IFN-γ enhance immune cell recruitment and cytokine secretion. The synergistic effects of these pro-inflammatory mediators lead to persistent inflammation, keratinocyte overactivity, and chronic plaque formation (31-33).

Advancements in psoriasis treatment

Understanding the pathophysiology of psoriasis has led to significant therapeutic advancements. Biologic therapies targeting IL-17, IL-23, and TNF-α have transformed disease management by disrupting key inflammatory pathways, reducing immune cell infiltration, and restoring immune homeostasis. These therapies not only improve skin lesions but also help mitigate systemic inflammation and associated comorbidities. However, challenges remain in identifying biomarkers for treatment response, necessitating further research into precision medicine approaches (35).

Treatment of psoriasis

The treatment of psoriasis has evolved with a range of therapeutic strategies. Currently available oral systemic therapies include retinoids like acitretin, which is effective with a PASI75 response of 47-53%, though it carries side effects like dry mouth and liver enzyme elevations (36). Methotrexate inhibits dihydrofolate reductase, offering a PASI75 response of 45.2%, but also presents risks such as nausea and liver issues. Cyclosporine A, a calcineurin inhibitor, shows a PASI75 response between 50-97% but can cause nephrotoxicity and increased infection risk. Apremilast, a PDE4 inhibitor, offers a PASI75 response of 33.1% but has side effects like diarrhea and depression. Biologic therapies include TNFα inhibitors like infliximab and adalimumab, with PASI75 responses around 80%, though they carry risks of infections and reactivation of conditions like hepatitis. IL23 inhibitors, such as Ustekinumab and Guselkumab, have demonstrated PASI75 responses ranging from 67.5 to 91.2%, with mild side effects such as nasopharyngitis. IL17 inhibitors like secukinumab and ixekizumab provide PASI75 responses between 77.1% and 90%, but with risks of candidiasis and other severe effects. RORγt inhibitors like VTP-43742, though promising, were halted due to liver toxicity (36-38). The IL36 receptor antagonist BI 655130 has been effective in treating generalized pustular psoriasis with symptom reduction over 20 weeks. JAK inhibitors, such as tofacitinib and baricitinib, block inflammatory signalling and show PASI75 responses of 39.5-81.1%, though they are associated with cardiovascular risks. Sphingosine-1-Phosphate (S1P) agonists like ponesimod also indicate efficacy with PASI75 responses of 46-77%, but with concerns over side effects like lymphopenia and bradycardia (39). The ROCK2 inhibitor KD025, which is still under study, shows potential in reducing psoriasis symptoms through inhibition of cell signalling pathways. This array of treatments reflects the broad spectrum of current therapeutic approaches for managing psoriasis. Basic pharmacological treatment is shown in table 3 (40).

Biomarkers in psoriasis

Insights for diagnosis and treatment: For biomarkers to be truly effective in the diagnosis and management of psoriasis, they should exhibit several essential characteristics. Specificity is paramount, as

Table 3. Basic pharmacological treatment

Treatment type	Drug	Mechanism of Action in Psoriasis	Key side effects
Oral systemic therapy	Acitretin (Retinoid)	- Retinoid that regulates gene transcription via nuclear receptors, reducing keratinocyte proliferation	Dry mouth, cheilitis, pruritus, teratogenicity, liver enzyme elevation
	Methotrexate (MTX)	- Inhibits dihydrofolate reductase, disrupting DNA synthesis and reducing T-cell proliferation and inflammation	Nausea, mouth ulcers, liver issues
	Cyclosporine A (CyA)	- Calcineurin inhibitor that inhibits T-cell activation by blocking cytokine production (e.g., IL-2)	Nephrotoxicity, hepatotoxicity, infection risk
	Apremilast	- PDE4 inhibitor that increases cAMP in immune cells, reducing pro-inflammatory cytokine production (e.g., TNFα)	Diarrhea, vomiting, depression
Biologic therapy	Infliximab, Adalimumab, Certolizumab (TNFα Inhibitors)	- Inhibit TNFα, a key inflammatory cytokine involved in the pathogenesis of psoriasis, reducing immune cell activation	Hepatitis reactivation, tuberculosis, lymphoma
	Ustekinumab, Guselkumab, Risankizumab, Tildrakizumab (IL23 Inhibitors)	- Target IL-23, a cytokine that plays a critical role in Th17 cell differentiation and inflammatory responses in psoriasis	Nasopharyngitis, respiratory infections
	Secukinumab, Ixekizumab, Brodalumab (IL17 Inhibitors)	- Target IL-17, a cytokine that promotes inflammation and keratinocyte activation in psoriasis	Candidiasis, neutropenia, suicidal tendencies (brodalumab)
Novel agents	Tofacitinib, Baricitinib (JAK Inhibitors)	- Inhibit Janus kinases (JAKs), which are involved in cytokine signaling pathways, reducing inflammation in psoriasis	Cholesterol changes, cardiovascular events
	Deucravacitinib	- Selective TYK2 (Tyrosine Kinase 2) inhibitor that blocks IL-23, IL-12, and Type I IFN signalling, key cytokine pathways in psoriasis	Upper respiratory infections, acne, mouth ulcers
	Ponesimod (S1P Agonist)	- Sphingosine-1 phosphate receptor 1 (S1PR1) agonist that modulates immune cell trafficking to reduce inflammation in psoriasis	Lymphopenia, bradycardia
	KD025 (ROCK2 Inhibitor)	- Inhibits Rho-associated kinase 2 (ROCK2), which is involved in cell migration and inflammatory signalling, potentially reducing psoriasis symptoms	Inhibits inflammation and cell migration

an ideal biomarker should be able to clearly identify psoriasis and distinguish it from other inflammatory skin conditions, such as eczema or seborrheic dermatitis. This ensures that the biomarker provides accurate results without false positives. Sensitivity is equally important, as it allows for the detection of psoriasis even in its early stages or subclinical forms, when the disease may not yet be visually apparent (41). Early detection is crucial for initiating timely interventions to prevent further progression. Additionally, reproducibility plays a critical role; biomarkers should produce consistent results across various laboratories and clinical settings to ensure the reliability and generalization of findings. Another key attribute is predictive power, which refers to a biomarker's ability to forecast the disease course, potential flare-ups, or response to treatment. This capability can guide therapeutic decisions and help personalize treatment plans for better outcomes (42). Finally, accuracy is necessary to ensure that the

biomarker reflects the underlying biological processes of psoriasis without interference from other health conditions, thus providing a true representation of the disease (43). The methods employed for biomarker detection should also meet certain standards to be effective in clinical practice. Robustness is essential, as the detection technique should yield consistent and reliable results even under varying laboratory conditions. This ensures the biomarker's applicability across both routine clinical practice and research settings. Standardization of detection methods is equally important to ensure uniform application across different healthcare environments, which supports the integration of biomarkers into clinical practice guidelines. Moreover, simplicity is a key factor in the adoption of detection methods. The assays for biomarker detection should be straightforward, reducing technical complexity and enhancing their feasibility for routine clinical use (44). Biomarkers play a crucial role in psoriasis management, offering significant applications in diagnosis, disease monitoring, and treatment optimization. They can assist in distinguishing psoriasis from other dermatologic conditions, enabling more accurate diagnosis and early intervention. Furthermore, biomarkers are vital in monitoring disease progression and assessing treatment efficacy. By tracking changes in biomarker levels over time, clinicians can identify flare-ups, anticipate future exacerbations, and adjust treatment plans accordingly. Additionally, certain biomarkers have the potential to predict a patient's response to specific therapies, such as biologic treatments, thereby facilitating personalized medicine (45). By identifying patients who are more likely to benefit from particular treatments, biomarkers can help optimize therapeutic regimens for improved outcomes.

Classification of biomarkers in psoriasis

Psoriasis is a multifaceted, chronic inflammatory disorder of the skin, characterized by excessive keratinocyte proliferation, immune dysregulation, and heightened cytokine activity. The pursuit of identifying biomarkers in psoriasis has become integral in understanding its complex pathogenesis and optimizing clinical management. Biomarkers in psoriasis can be broadly categorized into genetic, tissue-associated, soluble, comorbidity-related, and treatment-response biomarkers. These markers hold promise not only for enhancing diagnostic accuracy and evaluating disease progression but also for tailoring individualized therapeutic strategies and improving patient outcomes (46). The summary of biomarker shown in table 4.

Genetic biomarkers: The genetic basis of psoriasis has been extensively studied, unveiling several loci that influence susceptibility and disease severity. One of the most significant genetic markers identified is *PSORS1*, which encodes the *HLA-CW6* gene. This gene plays a pivotal role in T-cell activation, thereby initiating the inflammatory cascade responsible for the epidermal hyperplasia typical of psoriasis (47-49). The *HLA-CW6* allele is strongly linked to early-onset psoriasis and more severe disease phenotypes. In addition, genetic loci like *PSORS4*, associated with genes regulating keratinocyte differentiation, have been identified. *S100 calcium-binding proteins*, encoded by genes linked to *PSORS4*, are instrumental in inflammation and cellular stress, both of which are dysregulated in psoriatic skin. Furthermore, polymorphisms in genes such as *IL23R*, *IL12B*, *IL23A*, and *TNFAIP3*, central to the *Th17* immune response, have been implicated in psoriasis pathogenesis. Understanding these genetic factors not only advances insights into the mechanisms underlying psoriasis but also paves the way for targeted therapies aimed at modulating these immune pathways for improved disease management (50,51).

Tissue-associated biomarkers: Tissue-associated biomarkers offer a comprehensive understanding of psoriasis at the cellular and histopathological levels. The *Psoriasis Area Severity Index (PASI)* is a key clinical tool used to assess the extent and intensity of psoriatic lesions, thus quantifying disease severity. However, its limitations—such as inter-observer variability and time-consuming evaluations—necessitate the use of complementary diagnostic methods. Skin biopsy, for instance, remains indispensable in both diagnosis and prognosis. Histopathological analysis of psoriatic lesions often reveals several markers crucial for understanding the disease process. *Keratin 16 (K16)* is frequently upregulated in psoriatic skin, serving as

Table 4. Various types of biomarkers

Category	Biomarker	Role
Genetic biomarkers	PSORS1, HLA-CW6, IL23R, IL12B, IL23A, TNFAIP3	These genes are involved in the susceptibility and severity of psoriasis. They help identify genetic predisposition and guide immune-targeted treatments
Tissue-associated biomarkers	Keratin 16 (K16), CD31, VEGF	These markers are associated with cell proliferation, blood vessel formation, and inflammation in psoriatic lesions, which are valuable for assessing disease activity
Soluble biomarkers	hBD-2, S100A7, S100A8, S100A9, VEGF, LCN2, YKL-40	These markers are elevated in psoriatic skin and fluids, indicating immune system activation and chronic inflammation, helping monitor disease progression and therapeutic response
Biomarkers for comorbidities	GlycA, Psoriasin (S100A7), NT-proBNP, Catalase, LDL antibodies	These biomarkers provide insights into the risk of associated conditions like cardiovascular diseases, oxidative stress, and metabolic disorders in psoriasis patients
Biomarkers for treatment response	C-Reactive Protein (CRP), HLA-C06:02, IL-17	These markers track systemic inflammation and immune responses, aiding in the prediction of treatment outcomes and guiding personalized therapy for psoriasis

a reliable marker of keratinocyte proliferation and abnormal differentiation. Its expression correlates with disease activity, indicating its potential as a prognostic biomarker. Additionally, vascular changes in psoriatic lesions, such as increased angiogenesis, reflect ongoing inflammation. Markers like *CD31* and *VEGF* are used to evaluate angiogenesis in psoriatic plaques, further linking immune system activation to skin vascularity. These tissue-based biomarkers are indispensable for monitoring disease progression and assessing the effectiveness of therapies aimed at modulating inflammation and keratinocyte turnover (52,53).

Soluble biomarkers: Soluble biomarkers, detectable in body fluids like blood, offer a non-invasive means of monitoring disease activity and treatment response in psoriasis. Human Beta Defensins *(hBD-2)*, antimicrobial peptides, are significantly elevated in the lesional skin of psoriasis patients. These peptides play an integral role in the innate immune response by activating immune cells such as dendritic cells and neutrophils, which contribute to the chronic inflammation seen in psoriasis. Elevated levels of *hBD-2* correlate with disease severity, making it a promising marker for monitoring disease activity and treatment efficacy. Other soluble biomarkers, such as *S100 proteins* (specifically *S100A7*, *S100A8*, and *S100A9*), are upregulated in psoriasis and aid in the recruitment of immune cells to sites of inflammation (54,55). These proteins act as pro-inflammatory mediators, amplifying the immune response. Increased serum levels of *S100* proteins have been associated with greater disease severity, and thus, they may serve as indicators of active inflammation. Additionally, Vascular Endothelial Growth Factor (VEGF), involved in angiogenesis, contributes to the inflammatory milieu. Lipocalin-2 (LCN2) and YKL-40, two other soluble markers, reflect systemic inflammation and are linked to psoriasis and its comorbidities, particularly in relation to *IL-17* activity (56).

Biomarkers for Comorbidities: Psoriasis is frequently associated with comorbidities such as cardiovascular disease, metabolic syndrome, and obesity. Identifying biomarkers that predict the presence and risk of these comorbidities is essential for holistic management of psoriasis. *GlycA*, a marker of systemic inflammation, has been identified as a potential predictor of cardiovascular risk in psoriasis patients. Elevated GlycA levels correlate with psoriasis severity and the presence of cardiovascular comorbidities, suggesting its potential role in identifying patients at higher cardiovascular risk. Similarly, Psoriasin (S100A7), involved in the

inflammatory response, is elevated in psoriasis and has been implicated in both psoriasis pathophysiology and cardiovascular health. Elevated levels of NT-proBNP, a cardiac biomarker, are commonly found in psoriasis patients, indicating potential early cardiovascular dysfunction, including heart failure (57-63). Additionally, the increased oxidative stress in psoriasis contributes to a heightened risk of atherosclerosis. Biomarkers such as *catalase* and *LDL antibodies* are indicative of oxidative damage, further linking psoriasis to cardiovascular pathologies. These comorbidity-related biomarkers highlight the need for a comprehensive approach to managing psoriasis, addressing both cutaneous and systemic health (64-67).

Biomarkers for treatment response: The identification of biomarkers that predict treatment response is critical for optimizing psoriasis management. C-Reactive Protein (CRP) is widely used to assess systemic inflammation in psoriasis (68-71). Elevated *CRP* levels reflect active inflammation, whereas a decrease in CRP often signals clinical improvement, particularly with biologic therapies. Biological treatments targeting specific immune pathways, such as TNF-α inhibitors, have been shown to reduce CRP levels, correlating with symptom improvement. Furthermore, genetic markers like *HLA*-C06:02* have been associated with differential responses to treatment. Patients carrying the *HLA*-C06:02 allele tend to respond more favorably to biologics like Ustekinumab, which targets *IL-12* and *IL-23*, key cytokines in psoriasis inflammation [72,73]. Identifying *HLA*-C06:02* can help clinicians predict which patients are likely to benefit from such therapies, thus enabling more personalized treatment decisions. Moreover, monitoring the levels of Interleukin-17 (IL-17), a cytokine central to psoriasis inflammation, can provide valuable insights into treatment efficacy (74). A reduction in IL-17 levels following treatment is typically indicative of a favourable response, making it a useful biomarker for tracking disease progress and therapeutic success. Despite the potential of biomarkers in diagnosing and managing psoriasis, several challenges hinder their widespread use in clinical practice. Biomarkers like CRP, while useful for assessing inflammation, are non-specific and can be elevated in various inflammatory conditions, making it difficult to differentiate psoriasis from other diseases such as rheumatoid arthritis or Crohn's disease. Genetic markers such as PSORS1 and *HLA*-CW6 are valuable but exhibit ethnic variability, limiting their general applicability across diverse populations. Additionally, tools like the Psoriasis Area Severity Index (PASI) suffer from inter-observer variability, as different clinicians may assess disease severity differently, leading to inconsistent results. Early detection of psoriasis is also challenged by the sensitivity limitations of biomarkers like S100 proteins and hBD-2, which may not be elevated in the early stages of the disease. Furthermore, variability in detection methods and laboratory protocols can lead to inconsistent results, undermining the clinical utility of biomarkers. Finally, while biomarkers like IL-17 are associated with treatment responses, predicting individual outcomes remains complex due to the heterogeneity in patient reactions to therapies such as biologics, complicating the personalization of treatment.

Conclusion

The biomarkers discussed provide crucial insights into the pathophysiological mechanisms of psoriasis, encompassing genetic predisposition, immune dysregulation, and environmental factors. A comprehensive understanding of these biomarkers offers substantial promise for advancing personalized medicine. This knowledge allows clinicians to improve diagnostic accuracy, anticipate treatment responses, and effectively monitor disease progression. However, for these biomarkers to be adopted in routine clinical practice, researchers should validate them through large-scale, multi-center studies and incorporate them into standardized clinical protocols. Validated biomarkers hold the potential to transform psoriasis care by enabling precise, individualized therapeutic strategies that align with disease heterogeneity and patient response variability. By summarizing the mechanistic roles of these biomarkers in psoriasis pathogenesis, this review highlighted their clinical relevance and potential utility in disease monitoring and treatment optimization.

Ethical approval

As this manuscript is a review article based on

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Conflict of Interest

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