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Pathophysiology and natural based therapeutic strategies for psoriasis: Insights from promising clinical trials

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ABSTRACT

Psoriasis is a long-term autoimmune inflammatory ailment with a multifaceted pathophysiology altered by genetic tendency, environmental triggers, and immune system abnormalities. It is marked by excessive keratinocyte growth, immune dysfunction, and increased oxidative stress, contributing to persistent inflammation. Conventional therapies, including corticosteroids, immunosuppressants, and biologics, have limitations due to adverse effects and long-term safety concerns. This review explores the pathogenesis of psoriasis, highlighting immune response mechanisms, oxidative stress involvement, and the potential of natural compounds as therapeutic alternatives. Medicinal plants, phytochemicals, and biologically active components such as flavonoids, polyphenols, and alkaloids have revealed promising anti-inflammatory and immunomodulatory effects. Clinical studies suggest that these natural agents can regulate cytokine production, inhibit keratinocyte proliferation, and modulate oxidative stress pathways, offering a safer and more profitable approach to psoriasis controlling. This review further explores the molecular interactions between plant-based bioactive agents and immune mechanisms, paving the way for novel natural therapeutic strategies.

Keywords: *Autoimmune, Cytokines, Inflammation, Psoriasis, Phytochemicals, Psoriasis management.*.

BACKGROUND:

Psoriasis is a persistent autoimmune inflammatory condition with a significant genetic component, primarily affecting the skin *[1]*. It is associated with chronic inflammation, leading to irregular keratinocyte growth and differentiation. Worldwide, psoriasis impacts nearly 125 million individuals, representing 2–3% of the global population, with psoriatic arthritis occurring in approximately 10–30% of cases *[2]*. This disorder greatly affects the well-being of patients, frequently contributing to psychological healthiness challenges like anxiety, depression, and, in extreme cases, suicidal ideation. Although the precise underlying mechanisms of psoriasis are still being studied, it is generally familiar as an immune-mediated disorder, primarily driven by T cells, with T-helper cells singing a crucial character in disease progression *[3]*.

The prevalence of psoriasis differs across populations, with an estimated global occurrence of 2%. It is more frequently observed in Caucasians, less common in Asian populations, and least prevalent among Black individuals *[4]*. Additionally, psoriasis is extra widespread in cooler environments, particularly in northern areas, compared to warmer tropical areas. In Europe, occurrence rates vary between 0.6% and 6.5%, with higher frequencies in northern regions *[5]*. The disease can develop at any age, though research suggests its initial onset often falls between 15 and 20 years, with another peak between

55 and 60 years. However, delays in seeking medical attention and gradual symptom progression can obscure the precise onset age *[6, 7]*.

Psoriasis manifests in various clinical forms, these are plaque psoriasis (psoriasis vulgaris), inverse psoriasis, guttate psoriasis, pustular psoriasis, and erythrodermic psoriasis. Of these, plaque psoriasis is very normal, affecting up to 90% of cases instances. It is marked by elevated, inflamed lesions by silvery-white scales, typically found on the scalp, torso, and outer areas of the limbs *[8]*. Other types affect different areas, including skin folds and joints, and can lead to systemic inflammation, raising the likelihood of metabolic syndrome and cardiovascular diseases. Several triggers, including genetic predisposition, environmental influences, infections, obesity, and vitamin D3 deficiency, have been linked to psoriasis development *[8, 9]*.

Although standard treatments such as corticosteroids, immunosuppressants, and biologics are available, they often come with drawbacks like toxicity, immune suppression, and heightened infection risks, making them unsuitable for long-term use *[2]*. This has fueled interest in exploring safer, more effective alternatives.

Herbal remedies have gained attention for their potential in management psoriasis because of their ability to reduce inflammation and regulate immune responses. Various plant-derived compounds, including flavonoids, polyphenols, and alkaloids, possess properties that could help control psoriatic symptoms. Studies indicate that these phytochemicals can mitigate oxidative stress, suppress crucial inflammatory mediators, within TNF-α, IL-17, and IL-23, while too regulate keratinocyte activity. This review examines the role of medicinal plants, plant-based bioactive compounds, and natural formulations for managing psoriasis, focusing their modes of action and clinical efficacy, clinical effectiveness, and potential as safer, cost-efficient alternatives to existing therapies. Understanding how these natural compounds interact with immune pathways could open new avenues for plant-based treatment strategies for psoriasis.

Mechanism of psoriasis pathology:

Psoriasis is a multifaceted state influenced by multiple factors, including excessive skin cell proliferation, irregular keratinocyte maturation, persistent inflammation, and immune system dysregulation. One of its defining features is rapid DNA synthesis and a significantly shortened epidermal turnover cycle, leading to the accumulation of immature keratinocytes. During this abnormal differentiation, keratins 6 and 16 are highly expressed, while the typical markers of mature keratinocytes, keratins 1 and 10, are delayed in expression *[10]*. This disruption in skin stability is further worsened by the aggregation of immune cells, including neutrophils in the epidermis and surface dermal layer, along with CD8+ T lymphocytes in the dermal layer, all of which contribute to prolonged inflammation *[11]*.

At the core of psoriasis pathology is an aberrant immune response involving natural and acquired immunity. Immune cells, chiefly dendritic cells, macrophages, T lymphocytes, and neutrophils, drive inflammation through excessive cytokine production *[12]*. This imbalance leads to ongoing keratinocyte stimulation, creating a continuous cycle of inflammation and abnormal skin thickening. Key cytokines, like TNF-α, IL-17, IL-23, and IFN-γ, are heavily engaged in amplifying inflammatory pathways, thus promoting disease progression *[13, 14]*.

Recent research highlights the impact of genetic and epigenetic influences in psoriasis susceptibility. Genetic variations influence immune regulation, altering cytokine activity and keratinocyte function, thereby determining disease severity and progression. Additionally, epigenetic modifications—such as DNA methylation, histone alterations, and regulatory non-coding RNAs (including microRNAs and long non-coding RNAs)—further modify gene expression patterns, influencing immune activity and skin cell dynamics *[15, 16]*.

Moreover, the skin microbiome is believed to influence the development and development of psoriasis pathogenesis. Disruptions in microbial composition may trigger aberrant immune responses, exacerbating chronic inflammation and autoimmune responses associated with the condition. The interplay between environmental influences, genetic predisposition, and immune dysfunction underscores the complexity of this disease.

Taken together, psoriasis is a highly intricate disorder driven by immune dysregulation, genetic predisposition, epigenetic alterations, and environmental triggers. A deeper understanding of these mechanisms could help in developing targeted treatments that regulate immune function, restoring epidermal homeostasis, and improving disease outcomes *[17]*.

Immune response mechanism in psoriasis:

Psoriasis is an autoimmune condition primarily instigated by an overactive immune response, with genetic factors predisposition and external elements such as skin trauma, pathogens, and certain medications *[18]*. One of its defining features is long-term inflammation that demonstrated in excessive keratinocyte progress and abnormal differentiation. Histological examination of psoriatic lesions reveals epidermis thickening, along with influx of immune cells, are dendritic cells, macrophages, T lymphocytes, and neutrophils within the dermis *[19]*.

The formation of psoriatic plaques involves dual major cell styles: Epidermal keratinocytes and mononuclear leukocytes play a crucial role in psoriasis. Genetic activity within these cells is regulated by specific psoriasis-related genes *[20]*. Keratinocytes actively engage with immune cells, promoting leukocyte activation and lesion formation. This interaction

disrupts the balance natural and acquired immunity, with keratinocyte-derived factors playing a direct role in influencing T lymphocytes and dendritic cells *[21]*.

Several innate immune cells are involved in psoriasis, including neutrophils, plasmacytoid dendritic cells (pDCs), and CD11c+ dendritic cells. Neutrophils, which have a short lifespan, are constantly created in the bone marrow and secrete into circulation. Their migration to the epidermis is facilitated by chemokines like interleukin-8 (IL-8) and CXCL1, along with keratinocyte-derived proteins like S100A7, A8, and A9 *[21]*. Plasmacytoid dendritic cells, identified by BDCA-2+ and CD123+ antigen expression, produce elevated amounts of interferon (IFN) upon stimulation, significantly contributing to disease progression. CD11c+ dendritic cells, the predominant type in the dermis, are existent in greater figures in psoriatic skin and contribute to inflammation by producing tumor necrosis factor (TNF) and activated nitric oxide synthase (iNOS). These cells also secrete pro-inflammatory cytokines, including IL-23 and IL-20, which stimulate T cells and keratinocytes *[22]*. Additionally, a subset of CD11c+ dendritic cells expresses differentiation indicator like DC-LAMP and CD83, which enable them to present antigens and initiate adaptive immune responses *[23]*.

Psoriatic lesions contain a significant influx of T lymphocytes and mature dendritic cells, which interact with chemokines are CCL19, CCL21, CXCL12, and CCL18 to support localized T cell stimulation T cells within psoriatic plaques are categorized into helper T cells (TH) and cytotoxic T cells (TC) *[24]*. Some of these cells exhibit CD161 and another cytotoxic receptors, suggesting that natural killer T cells in disease progression. *[25]*. Keratinocyte-derived factors perpetuate immune triggering response, while triggered immune cells modulate keratinocyte behavior by inducing adhesion molecule expression. Toll-like receptor (TLR) activation by heat shock proteins (HSPs) or S100A12 can initiate dendritic cell activation and maturation. Additionally, peptide antigens can trigger both innate and adaptive T cell reactions, indicating the occurrence of particular T cell clones in psoriatic lesions *[26, 27]*.

A crucial component of psoriasis pathogenesis is the dysregulation of IL-36 signaling. IL-36 cytokines (IL-36α, IL-36β, and IL-36γ), that belong to the IL-1 family, are significantly elevated in psoriatic plaques, where they regulate neutrophil-attracting chemokines like CXCL1 and CXCL8 *[28]*. The IL36RN gene encodes IL-36 receptor antagonists (IL-36Ra), which function as inhibitors of IL-36 signaling and prevent excessive inflammation. Genetic mutations in IL36RN have been linked to generalized pustular psoriasis (GPP), emphasizing the importance of IL-36 dysregulation in psoriatic inflammation. A deficiency or malfunction in IL-36Ra leads to unregulated IL-36 activity, further amplifying neutrophil infiltration and cytokine release, exacerbating disease severity *[29]*.

Persistent immune activation and defective regulatory T cell function contribute to chronic inflammation in psoriasis. Cytokine interactions in the disease follow a complex network, with key mediators including TNF, lymphotoxin (LT), IL-1, IL-17, IL-20, IL-22, and IFN. These signaling molecules activate transcription elements like STAT1 and NF-κB, reinforcing inflammation *[14]*. Dendritic cells further amplify inflammation through interactions with IFN, IL-20, IL-12, and IL-23, leading to T cell-driven cytokine synthesis. Additionally keratinocytes and stromal cells release cytokines including TGF-β, IL-1, IL-6, and IL-20, which regulate cellular communication and regulating epithelial-stromal interactions in psoriatic lesions *[30]*. Moreover, an intricate network of chemokine interactions exists, with numerous chemokines exhibiting elevated expression, indicating multiple regulatory pathways in psoriasis pathogenesis *[31]*.

Understanding these molecular mechanisms is vital for designing targeted therapeutic approaches aimed at reducing inflammation and immune dysregulation in psoriasis (figure 1).

Figure1: Regulatory action of flavonoids on inflammatory signaling pathways in psoriasis

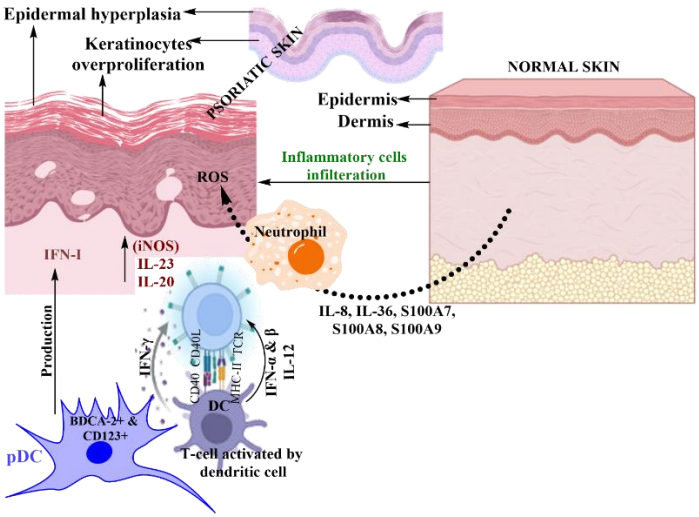

Fig.1: Pictorial presentation of the immune response mechanism in psoriasis: role of inflammatory cytokines and effects contributing to keratinocyte hyperproliferation.

Oxidative stress in psoriasis progression: Recent research highlights the significant role of reactive oxygen species (ROS) and nitric oxide species (NOS) in the development of psoriasis. The disruption of redox homeostasis, along with increased production of stimulated NOS, leads to oxidative stress, that significantly contributes to disease advancement. Understanding the molecular pathways through which these oxidative molecules drive inflammation may provide valuable insights for therapeutic interventions. Targeting dysregulated oxidative stress mechanisms using naturally derived antioxidants presents a promising strategy for developing novel treatments for psoriasis.

Reactive Oxygen Species (ROS) and their role in psoriasis: Reactive oxygen species (ROS) are oxygen-containing compounds capable of interacting with biological substrates. They are classified into radical species—including hydroperoxyl (HO_2•), superoxide (O_2•$^-$), hydroxyl (OH•), and peroxyl radicals (RO_2•), and non-radical species like ozone (O_3), hydrogen peroxide (H_2O_2), and hypochlorous acid (HOCl), which can readily transform into radical forms *[32]*.

Molecular oxygen in its triplet state has two electrons with identical spins, allowing it to accept electrons individually. When oxygen undergoes excitation, and experiences an electron spin reversal, it becomes more reactive and interacts with compounds containing double bonds *[33, 34]*. ROS are generated through enzymatic metabolic activities as well as external influences such as radiation and xenobiotics. Mitochondrial respiration is a primary ROS source, where oxygen undergoes sequential reduction in the electron transport chain, forming water. However, during this process, ROS may be released. Peroxisomal metabolism also contributes to ROS production through oxidative reactions that remove hydrogen from biomolecules, forming hydrogen peroxide. Leukocyte NADPH oxidase pivotal role in immune defense by rapidly producing ROS during oxidative bursts, while non-enzymatic ROS formation occurs due to ultraviolet radiation exposure *[33-37]*.

Nitric Oxide Synthases (NOS) and Psoriasis pathogenesis:

Nitric oxide synthases (NOS) are enzymes that facilitate the generation of nitric and exist in three distinct systems: endothelial NOS (eNOS), neuronal NOS (nNOS), and stimulated NOS (iNOS). Both eNOS and nNOS are continuously expressed and require calcium ions for activation, while iNOS is inducible and calcium-independent.

In psoriasis, iNOS is overexpressed in keratinocytes, promoting oxidative stress *[38]*. The active NOS form is a homodimer utilizing NADPH, molecular oxygen, and L-arginine as substrates, with cofactors such as flavin mono nucleotide (FMN), flavin adenine dinucleotide (FAD), tetrahydrobiopterin (BH4), and calmodulin. This enzyme first converts L-arginine into N-hydroxy-L-arginine, which undergoes further oxidation to produce nitric oxide (NO) and L-citrulline *[39]*. Excess NO reacts with superoxide (O_2•$^-$) forming peroxynitrite ($ONOO^-$), a highly reactive nitrogen species (RNS) inducing cellular damage by modifying proteins, lipids, and nucleic acids.

Oxidative stress occurs when ROS production outstrips the ability of antioxidant protective processes, leading to impaired redox signaling and cellular damage *[40]*. Elevated ROS levels are linked to DNA damage, lipid degradation and the secretion of inflammatory signaling molecules. Low ROS levels regulate physiological signaling, while excessive ROS production triggers inflammatory responses, cellular dysfunction, and apoptosis *[37, 41-43]*.

Oxidative Stress in Psoriasis Progression

The collaboration between reactive oxygen species (ROS), reactive nitrogen species (RNS), and diminished antioxidant defenses plays a pivotal role in the development of psoriasis. The body relies on enzymatic antioxidants are superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) mitigate oxidative damage, while non-enzymatic antioxidants like vitamins C and E and glutathione (GSH) neutralize oxidative stress. Antioxidant enzyme activity fluctuates in psoriatic tissues, with declining vitamin E and GSH levels *[39, 40, 44, 45]*.

Mild oxidative stress is more relevant to psoriasis development than severe oxidative damage. Oxidative stress markers like total oxidative stress (TOS) and malondialdehyde (MDA) levels in plasma or serum, tend to rise in parallel with increased disease severity as assessed by the PASI. In contrast, antioxidant markers tend to show an inverse relationship with disease progression *[44-47]*. Oxidative stress has been shown to influence several molecular pathways, including those regulated by tumor necrosis factor-alpha (TNF-α). Signaling pathways including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), mitogen-activated protein kinases (MAPK), and Janus kinase/signal transducer and activator of transcription (JAK-STAT) play major roles in this process. These pathways stimulate the differentiation of T helper (Th) cells, mainly T h1 and Th17 subgroups, resulting in increased inflammatory cytokine production, enhanced keratinocyte proliferation, recruitment of immune cells, and abnormal angiogenesis due to lipid peroxidation *[37, 48-50]*.

The process of lipid peroxidation alters the balance between cyclic nucleotides, elevating cyclic guanosine monophosphate (cGMP) while reducing cyclic adenosine monophosphate (cAMP), thereby leading to excessive epidermal proliferation. Psoriasis patients exhibit high oxidized low-density lipoprotein (ox-LDL) and increased phospholipase A2 (PLA2) activity *[51]*. ROS influence intracellular calcium levels, impairing cell differentiation, proliferation, and apoptosis *[51, 52]*.

Oxidative stress also recruits myeloid dendritic cells (mDCs), which drive immune responses by producing interleukin-8

(IL-8) and TNF-α, elevating T-cell proliferation. ROS promote Th1 cells leading to increased production of inflammatory cytokines like interferon-gamma (IFN-γ) and interleukin-2 (IL-2) within psoriatic lesions *[53, 54]*. Oxidative stress upregulates vascular endothelial growth factor (VEGF), *[55, 56]*, contributing to abnormal angiogenesis and leukocyte migration, exacerbating inflammation *[57]*.

ROS modulate MAPK pathways, including mitogen-activated protein kinase (MAPK) cascades such as extracellular signal-regulated kinases (ERKs), c-Jun N-terminal kinases (JNKs), and p38 MAPKs, all of which perform a role in psoriasis progression *[58, 59]*. The influence of ROS on (NF-κB) signaling varies depending on cellular conditions, as ROS can either activate or inhibit this pathway *[59, 60]*. Elevated phosphorylated NF-κB and ROS in psoriatic tissues indicate that oxidative stress drives NF-κB activation. Additionally, ROS influence JAK-STAT signaling in human lymphocytes, implicating it in psoriasis pathogenesis *[61]*.

Oxidative stress is a critical feature in both the beginning and expansion of psoriasis, by influencing inflammation, and epidermal hyperproliferation. A deeper understanding of these molecular interactions can facilitate the development of innovative treatments strategies intended at justifying oxidative stress and its impact on psoriasis development.

Natural substances (natural sources, phytochemicals, and plants) for the treatment of Psoriasis:

Recent research on novel therapies has highlighted natural compounds highlighting, their wide availability, safety, and efficacy in managing psoriasis *[62]*. Clinical investigations have shown that certain naturally derived substances can help alleviate psoriasis through mechanisms such as promoting apoptosis, inhibiting angiogenesis, and reducing inflammation. These beneficial effects are primarily attributed to their ability to counteract oxidative damage triggered by ROS and suppress the excessive construction of stimulated nitric oxide synthase, which shows a crucial character in inflammatory signaling pathways associated with psoriasis *[63]*.

Omega-3-sources: Psoriasis is a chronic inflammatory skin disorder driven by an overactive immune response, particularly involving T-cells, inflammatory mediators, and cytokines. A major contributor to psoriasis is the disruption in the equilibrium between pro-inflammatory and anti-inflammatory eicosanoids, leading to excessive keratinocyte growth and compromised skin barrier function *[9]*.

Omega-3 polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), found in fish oil, can help modulate this immune response. They compete with arachidonic acid (ARA) in cell membranes. Thus, they assist decrease the synthesis of inflammatory eicosanoids like leukotriene B4 (LTB4) and prostaglandins, which drive psoriasis-related inflammation. Additionally, omega-3s promote the formation of specialized pro-resolving mediators (SPMs) like resolvins, that support control neutrophil migration and inflammatory cytokine release *[64]*.

Research indicates that omega-3 supplementation may decrease systemic inflammation, improve the skin barrier, and decrease cytokine levels including TNF-α, IL-6, and IL-17, these are main drivers of psoriasis. Moreover, *Annona squamosa* seed extract, rich in linoleic acid (LA) and oleic acid (OA), has shown potential in inhibiting keratinocyte proliferation, mimicking the effects of corticosteroids without side effects. Although results vary in human studies, omega-3 supplementation could serve as a complementary approach to psoriasis management, helping reduce symptom severity and associated comorbidities like obesity and insulin resistance *[9, 65]*.

Vitamin D: Vitamin D shows a fundamental role in modulating immune function and maintaining skin by activating the Vitamin D Receptor (VDR), which subsequently binds with the Retinoid X Receptor (RXR) to regulate gene expression. This process influences key genes such as CYP27B1, which helps conversion of vitamin D into its bioactive form for localized immune modulation, and IL10, which enhances the production of the anti-inflammatory cytokine IL-10 while inhibiting pro-inflammatory cytokines like TNF-α, IL-8, IL-2, IFN-γ, and IL-17. During psoriasis, vitamin D helps normalize keratinocyte differentiation by upregulating KRT1 and KRT10, while suppressing KRT6 and KRT16, which contribute to excessive proliferation. It also restores the distribution of ICAM-1, HLA-DR, and CD26, improving keratinocyte adhesion and reducing inflammation. These effects collectively modulate T-cell responses, normalize epidermal turnover, and restore skin barrier integrity, making vitamin D a valuable therapeutic option for psoriasis *[9]*.

Vitamin E: Vitamin E a fat-soluble antioxidant, crucial for cell membrane stability, with α-tocopherol being its most active form. Research indicates that individuals with psoriasis, especially those with severe symptoms or chronic alcohol consumption, often exhibit significantly reduced plasma and tissue vitamin E levels. This finding suggests a connection between oxidative imbalances and psoriasis progress. Oxidative imbalance arises when discrepancy between free radicals (reactive oxygen species) and the body's antioxidant defenses leads to cellular damage and inflammation. In psoriasis, increased oxidative stress damages keratinocytes and immune cells, stimulating excessive discharge of inflammatory cytokines are TNF-α and IL-6, that accelerate skin cell proliferation. Low vitamin E levels weaken the body's antioxidant defense, worsening oxidative damage and contributing to psoriasis severity *[66]*.

A randomized study involving 60 patients with autoimmune skin disorders, including psoriasis, alopecia areata, and vitiligo, found reduced vitamin E concentrations compared to healthy individuals. Another clinical trial involving psoriatic arthritis (PsA) and erythrodermic psoriasis (EP) assessed the impact of an antioxidant supplement containing vitamin E, selenium,

and Coenzyme Q10 alongside standard treatments *[67]*. The supplemented group showed significantly faster clinical improvement and reduced disease severity within 30 days *[68]*.

Additionally, another investigation evaluated the impact of a dietary antioxidant mixture, including vitamin E, selenium, and Coenzyme Q10, on individuals with severe psoriasis to determine its potential role in disease management *[9, 67]*

Medicinal plant species role in Psoriasis treatment:

Aloe vera: Aloe vera, a succulent plant widely recognized for its medicinal applications, has been traditionally utilized to address various dermatological conditions. Its gel extract is widely incorporated into cosmetics, pharmaceuticals, and supplements due to its rich composition of anthraquinones, polysaccharides, vitamins, salicylic acid, carotenoids, and flavonoids. These bioactive compounds help soothe itching and reduce inflammation associated with psoriasis.

Studies have shown that Aloe vera extracts from both the gel and leaves influence inflammatory signaling pathways by preventing NF-κB, MAPK, and PI3K activation, while also decreasing the formation of iNOS, IL-6, and IL-1 in cells (macrophages cells). Furthermore, Aloe vera is known to be reduce prostaglandin E2 levels by inhibiting cyclooxygenase (COX) activity. Studies using on psoriatic HaCaT cells (a keratinocyte model) stimulated with TNF-α showed that *Aloe vera* at dosing of 20, 40, and 80 µg/mL for 24 hours, improved cell sustainability and reduced inflammatory responses *[69, 70]*.

Angelica Sinensis (Dong Quai, Female Ginseng)

Angelica sinensis, widely known as Dong Quai or female ginseng, is a biennial or perennial plant from the Apiaceae family. Traditionally employed in Chinese medicine, it is considered to refill blood and address deficiencies. The plant contains psoralen, a potent furocoumarin with photosensitizing properties used in psoriasis treatment.

Psoralens enhance UV-A exposure effects, slowing epidermal DNA synthesis through DNA cross-linking. This mechanism underlies PUVA therapy, where patients ingest Angelica sinensis extract before UV-A exposure. Psoralens also induce mitochondrial dysfunction, Langerhans cell toxicity, oxidative stress, and programmed cell death in keratinocytes and lymphocytes *[71]*.

A controlled, double-blind study assessed oral psoralen with UV-A therapy in individuals with plaque psoriasis, measured by the PASI score. After twelve weeks, two-thirds of treated patients showed at least a 75% improvement, while the placebo group showed no significant change *[72]*.

Artemisia capillaris:

Artemisia capillaris, a traditional herbal remedy in East Asia, has been historically used to treat fever and liver disorders. It contains various bioactive compounds, including chlorogenic acids, coumarins, and flavonoids, which have shown therapeutic potential against conditions like cancer, hepatitis, malaria, obesity, and infections *[73]*. In psoriasis treatment, Artemisia capillaris extract has demonstrated the ability to suppress excessive keratinocyte proliferation and induce apoptosis. Additionally, it may help in reducing leukocyte infiltration by downregulating ICAM-1 expression and suppressing nitric oxide production through the prevention of iNOS activity *[74]*. Studies evaluating its effects on psoriasis used varying doses (ranging from 1 to 100 µg/mL) of *Artemisia capillaris* extract on HaCaT cells over a 72-hour period. Further investigations focused on a 50 µg/mL dose, testing its efficacy together ex vivo and in vivo trials using IMQ-stimulated psoriatic models in HaCaT cells and mice *[75]*.

Rehmannia glutinosa:

This is recognized for its strong antioxidant capabilities, aiding in the deactivation of free radicals and reducing oxidative imbalance. Research suggests that it can inhibit iNOS expression and the secretion of proinflammatory cytokines, including TNF-α, IL-6, IL-17A, and IL-23. Additionally, it may help lower PGE2 levels by inhibiting COX-2 activity and modulate chemoattractant expression, such as CCL2 and CXCL10, potentially through suppression of the JAK-STAT signaling mechanism.

Animal model research involved administering Rehmannia glutinosa extract at concentration of 100 µg/g and 200 µg/g body weight over a seven-day period. In vitro experiments utilized doses of 100 µg/mL, 500 µg/mL, and 1000 µg/mL for 24 hours. These effects were further supported by in vivo studies using an IMQ-induced psoriasis model in mice and in vitro experiments on THP-1 and RAW264.7 cells, where inflammation was induced via LPS stimulation *[76, 77]*.

Salvia miltiorrhiza:

Salvia miltiorrhiza has drawn significant research interest owed to its anti-inflammatory, antioxidant, and antiproliferative possessions, alongside its potential protective properties. It is also considered to have antipsoriatic potential. Investigations on HaCaT cells treated with IL-1, IL-17, IL-22, and oncostatin M, as well as in animal model involving an IMQ-induced psoriasis model in mice, demonstrated that *Salvia miltiorrhiza* root extract could help mitigate inflammation by neutralizing free radicals and suppressing Akt and ERK1/2 phosphorylation. This herbal extract found to decrease skin wound thickness, minimize scaling, and constrain excessive keratinocyte proliferation while concurrently promoting apoptosis, making it a

potential candidate for psoriasis management. While its exact mechanism of action remains under study, it may function by interfering with yes-associated protein (YAP) signaling and/or inhibiting STAT3 activation *[78, 79]*.

Capsicum annuum:

Capsicum annuum, is associated with psoriatic itching is linked to neuropeptides such as neuropeptide Y, PGP 9.5, NGF, CGRP, and SP, which are elevated in affected skin. Increased levels of NGF and SP in keratinocytes and nerve fibers correlate with itch intensity in psoriasis. Capsaicin, a bioactive compound in *Capsicum annuum*, has shown effectiveness in reducing psoriasis-related itching by modulating neuropeptide activity, suggesting its potential therapeutic role in managing psoriatic symptoms *[80, 81]*.

In vitro tests utilized concentrations of 0.125, 0.25, and 0.5 mmol/L, revealing that the extract can help reduce skin lesion thickness, minimize scaling, and inhibit keratinocyte overgrowth while enhancing apoptosis —a crucial factor in psoriasis treatment. Though the precise mechanism remains unclear, it is hypothesized to involve the inhibition of YAP and/or STAT3 activation, which are key pathways in psoriasis progression *[81]*.

Flavonoids compounds: Flavonoids, a diverse group (Figure 2) of polyphenolic components, highly regarded for their potent antioxidant and anti-inflammatory properties. These features create them capable nominees for treating inflammatory conditions such as psoriasis *[82]*. Over the years, increasing evidence has highlighted the effectiveness of these natural compounds to alleviating psoriatic symptoms by targeting key inflammatory pathways and oxidative stress (figure 3) *[83]*.

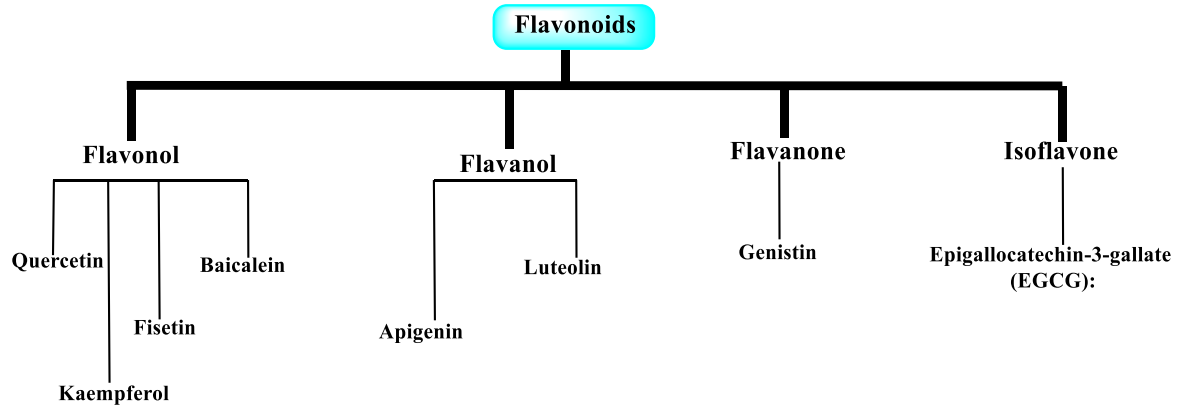

Fig. 2: Visual representation of the major classes of flavonoids

Baicalein:

It is a flavone extracted from *Scutellaria baicalensis*, and *Rhus mysorensis* exhibits notable anti-inflammatory, antioxidant, and keratinocyte-regulating possessions. Its healing effects stem from its talent to restrainNF-κB pathway, thereby decreasing the stages of essential pro-inflammatory cytokines like IL-6 and TNF-α, that are critical in psoriasis pathogenesis. Additionally, baicalein has been found to inhibit macrophage activation and infiltration, thereby limiting the secretion of Inflammatory signaling molecules like COX-2 and NF-κB, which are responsible for exacerbating psoriatic inflammation. Studies suggest that *S. baicalensis* extract contributes to epidermal thinning and minimizes oxidative imbalance by stimulating the Nrf2/HO-1 pathway, a crucial mechanism for cellular defense. These multifaceted effects position baicalein as a promising candidate for long-term psoriasis management *[84, 85]*.

Fisetin: Fisetin (3,7,3′,4′-tetrahydroxyflavone) is a flavonol naturally present in several fruits and veges, documented for its antioxidant, anti-inflammatory, and pro-apoptotic action. Research indicates that fisetin inhibits the mTOR pathway, enhances autophagy markers (LC3A/B, Atg5), and lowers IL-17A levels in CD4+ T cells, a major contributor to psoriasis. In an in vivo model of psoriasis induced by imiquimod, topical application of fisetin led to a reduction in IL-17A expression. Akt/mTOR pathway modulation, and improve keratinocyte maturation and autophagic processes, effectively mitigating psoriatic symptoms. Furthermore, studies utilizing a 3D human skin model (FTRHSP) demonstrated that fisetin not only reduced disease-like manifestations but also decreased IL-17 secretion in CD4+ T lymphocytes, highlighting its potential for treating inflammatory skin conditions. Mechanistically, fisetin exerts its effects through PI3K-Akt-mTOR and p38/JNK pathway modulation, reinforcing its potential as a cost-effective therapy for psoriasis and related disorders *[86, 87]*.

Quercetin: A naturally occurring flavonoid present in *Ginkgo biloba [88]*, *Rhus mysorensis [89]* and *Hypericum perforatum [90]*, Its possess antioxidant, anti-inflammatory, and immune-modulating effects *[91]*. Research indicates that quercetin can influence inflammatory pathways, particularly MAPK and NF-κB, revealed in C6 glioma cell studies *[92]*. In experimental psoriasis models, quercetin supplementation at doses of 30 µg/g, 60 µg/g, and 120 µg/g over 7 days resulted in marked reductions in pro-inflammatory cytokines, containing TNF-α, IL-6, and IL-17, all of that contribute to psoriatic inflammation. Furthermore *[93]*, quercetin has been found to promote orthokeratosis, modulate epidermal thickness, and suppress

inflammatory responses, underscoring its role in immune regulation and psoriasis symptom relief. These findings suggest that quercetin holds therapeutic capacity for managing prolonged inflammatory skin diseases like psoriasis.

Apigenin: Apigenin, a flavonoid abundant in parsley, thyme, celery, onions, sweet peppers, and tea *[94]*, possess anti-inflammatory, antioxidant, and antibacterial possessions, assemble it a capable contender for psoriasis management. Its therapeutic effects stem from its talent to prevent NF-κB stimulation, a crucial modulator of inflammation and autoimmune responses. Studies have demonstrated that administering 5 µmol of apigenin significantly reduces IL-6 and IL-12 levels, both are elevated in psoriasis, thereby alleviating inflammation and immune dysregulation *[95]*.

Further research highlights apigenin's efficacy in reducing Psoriasis Area and Severity Index (PASI) and CosCam level, improving histological features of psoriasis, and downregulating CCR6, IL-17A, and NF-κB expression. It effectively modulates the IL-23/IL-17/IL-22 axis, a critical pathway in psoriatic inflammation, and suppresses NF-κB nuclear translocation in LPS-induced macrophage cells, preventing excessive immune responses. Additionally, apigenin exhibits anti-proliferative effects on keratinocytes, as shown in HaCaT cell studies, limiting the abnormal cell growth characteristic of psoriatic lesions. Acute dermal toxicity studies confirm its safety for topical use, positioning apigenin as a potential natural treatment for psoriasis by addressing inflammation, immune modulation, and keratinocyte proliferation *[96]*.

Figure 3: Pictorial presentation of the immune response mechanism in psoriasis: role of inflammatory cytokines and effects contributing to keratinocyte hyperproliferation.

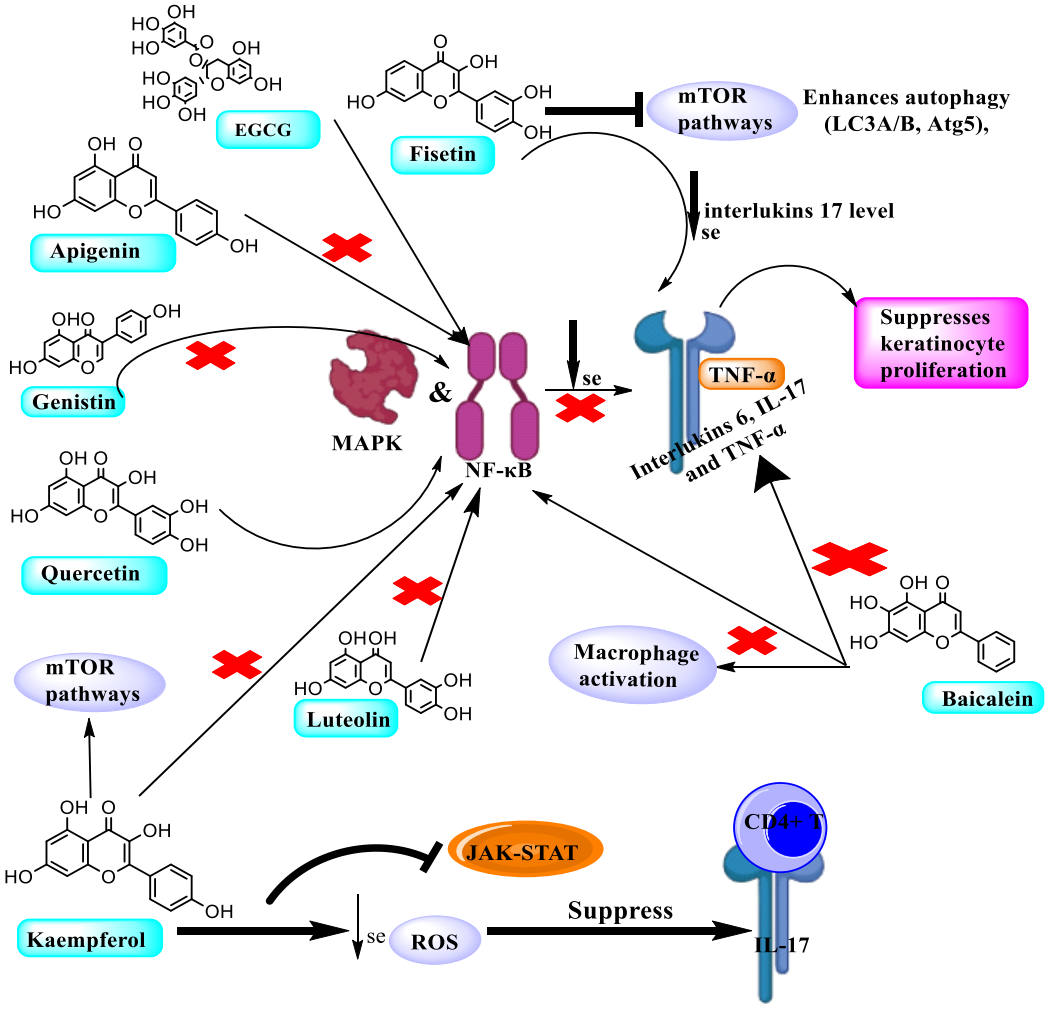

Fig. 3: Regulatory action of flavonoids on inflammatory signaling pathways in psoriasis.

Kaempferol: Kaempferol, a flavonoid naturally present in various fruits and veges, is known for its potent anti-inflammatory and immunomodulatory action, Indicating its potential as a psoriasis therapy. Research indicates that kaempferol effectively mitigate oxidative stress by decreasing intracellular ROS levels and modulating key inflammatory pathways. It has been shown to suppress IFN-γ- triggered JAK-STAT mechanism by downregulating IFN-γR1 production while upregulating SOCS1, thereby suppressing excessive immune activation *[97]*.

In psoriasis models, kaempferol alleviated IMQ-induced skin lesions by decreasing dendritic cell infiltration and γδT17 cell populations while suppressing pro-inflammatory cytokines like IL-23, IL-17A, TNF-α, IL-6, and IL-1β. Additionally, it decreased NF-κB phosphorylation, further contributing its role in reducing inflammation *[98]*.

Kaempferol also promoted immune regulation by increasing FoxP3+ regulatory T cell (Treg) populations in lymphoid organs and psoriatic skin, while inhibiting IL-17A+ CD4+ T lymphocytes and suppressing mTOR signaling. The downregulation of inflammatory mediators and reduction of CD3+ T cell infiltration further reinforce its function in immune regulation *[98]*.

Through these mechanisms, kaempferol effectively mitigates psoriasis by modulating key inflammatory and immune pathways, positioning it as a promising agent for psoriasis management.

Luteolin: Luteolin, a polyphenolic flavonoid originate in herbs and veges like artichokes, celery, and green peppers, is broadly familiar for anti-inflammatory, antioxidant, and immune-modulating effects. Its therapeutic potential lies in its ability to inhibit key inflammatory mechanism, concluding NF-κB, STAT3, and AP-1, resulting in decreased levels of pro-inflammatory cytokines are TNF-α, IL-6, IL-8, and IL-17, which are crucial in psoriasis development. Additionally, luteolin helps counter oxidative pressure by stimulating the Nrf2/HO-1 mechanism, which aids in neutralizing reactive oxygen species (ROS) and shielding keratinocytes from oxidative harm, a major contributor to psoriasis progression. Furthermore, it suppresses the over activation of the NLRP3 inflammasome, reducing immune cell infiltration and excessive inflammation. By modulating keratinocyte growth and maturation, luteolin helps reestablish epidermal equilibrium, resulting in the reduction of psoriatic lesions. Experimental studies on human keratinocytes (HaCaT cells) and In vivo psoriasis models have revealed its efficacy in decreasing inflammatory damage and improving skin health *[99]*. Given its multi-targeted approach in regulating inflammation, oxidative stress, and immune responses, luteolin holds significant therapeutic promise for psoriasis treatment, warranting further clinical investigations to validate its effectiveness *[99, 100]*.

Genistein: Genistein, a flavonoid abundant in soybeans and fava beans, exhibits potent antioxidant, anti-inflammatory, and immunomodulatory effects, positioning it as a possible therapeutic option for psoriasis *[101, 102]*. Research has possessed that genistein can suppress key pro-inflammatory cytokines, which IL-1β, IL-6, TNF-α, CCL2, IL-17, and IL-23, in psoriasis models. It suppresses STAT3 phosphorylation and inhibits NF-κB stimulation by preventing IκB phosphorylation and NF-κB nuclear translocation in TNF-α-stimulated keratinocytes, thereby mitigating inflammatory responses *[103]*.

Additionally, genistein counteract oxidative stress- driven NF-κB activation and cytokine release in keratinocytes by decreasing ROS production. In vitro studies conducted together common and psoriasis-like keratinocytes have demonstrated that genistein modulates disease-associated gene expression and improves psoriasis-related transcriptional alterations. Notably, it downregulates IL-8, IL-20, and CCL2 expression at both RNA and protein levels while preventing TNF-α and cytokine-induced NF-κB translocation, without affecting the PI3K signaling pathway *[104]*.

Through these mechanisms, genistein effectively regulates inflammatory signaling, reduces oxidative stress, and modulates gene expression associated with psoriasis progression, genistein emerges as a potential therapeutic option for managing this chronic inflammatory skin situation.

Epigallocatechin-3-gallate (EGCG): This is a prominent flavonoid observed in green tea, quercetin, and black tea *[105]* derivatives, exhibits strong anti-inflammatory, antioxidant, and immunomodulatory effect, constructing this is a probable therapeutic agent for psoriasis. Its therapeutic potential in psoriasis is attributed to its ability to regulate epidermal cell proliferation and oxidative stress. Studies using imiquimod (IMQ)-induced psoriasis models have shown that EGCG application significantly decreases PCNA expression, inhibits excessive keratinocyte proliferation, and improves pathological skin structure. Furthermore, EGCG enhances the skin's antioxidant guard system by accumulative the action of superoxide dismutase (SOD) and catalase (CAT) while reducing oxidative damage markers such as malondialdehyde (MDA) *[105]*.

EGCG also modulates immune responses by reducing T-cell infiltration, suppressing CD11c(+) dendritic cell populations in the spleen, and lowering pro-inflammatory cytokine levels, containing IL-17A, IL-17F, IL-22, and IL-23. Concurrently, it promotes immune balance by enhancing the number of CD4(+) T cells in the spleen. Through these mechanisms, EGCG mitigates psoriasis-related inflammation, oxidative stress, and abnormal epidermal proliferation, highlighting its therapeutic potential for psoriasis management *[105, 106]*.

Polyphenolic compounds as antipsoriatic:

Resveratrol: Resveratrol is a found naturally stilbenoid polyphenol commonly originate in grapes, berries, and *Polygonum cuspidatum*, is familiar for its potent antioxidant and anti-inflammatory activity, positioning it as a possible therapeutic compound for psoriasis *[107]*. In an animal study by IMQ-generated psoriasis model have shown that resveratrol reduces key pro-inflammatory cytokines such as IL-17A, IL-19, and IL-23 while facilitating keratinocyte apoptosis. These effects are expected to be linked with SIRT1 activation and the inhibition of Akt kinase, both of which regulate cellular survival and inflammatory processes.

In an *in vitro* experiments on NHEK cells demonstrated that resveratrol effectively suppresses epidermal proliferation and inhibits aquaporin 3 (AQP3), which plays a role maintaining skin hydration and barrier function. Additionally, in silico modeling and In vivo studies revealed that ε-viniferin, a resveratrol derivative, accumulated more efficiently in psoriatic skin and exhibited superior anti-inflammatory effects by reducing IL-23 secretion more effectively than resveratrol. These observations show the capability of resveratrol and its derivatives in managing psoriasis symptoms by modulating keratinocyte function, suppressing inflammatory cytokines, and enhancing skin barrier integrity *[108, 109]*.

Curcumin: Curcumin is a biologically active components naturally present in turmeric, is well recognized for its strong anti-inflammatory, antioxidant, and immune-regulating effects, making it a potential treatment option for psoriasis *[110]*. Molecular docking studies indicate that curcumin interacts directly with TNF-α, potentially interfering with its signaling pathways and reducing inflammation. Additionally, *In vivo* research shows that curcumin can modulate immune responses by lowering the expression of TLR2, TLR4, and TLR9, that show key roles in inflammatory signaling. Activation of SIRT1 and inhibition of Akt kinase contribute to the downregulation of pro-inflammatory cytokines and concurrently enhance the production of IL-10, an anti-inflammatory cytokine instrumental in reestablishing immune equilibrium *[111, 112]*.

In vitro experiments further reveal that curcumin suppresses TNF-α-induced IL-1β, IL-6, and TNF-α expression in HaCaT cells by preventing the MAPK and NF-κB signaling mechanism. It also impedes keratinocyte proliferation and NF-κB activation, essential contributors to psoriasis pathology *[113]*. Furthermore, curcumin believed as a effective inhibitor of phosphorylase kinase (PhK), an enzyme linked to psoriatic activity, suggesting its potential for topical applications. Clinical trials indicate its safety, though higher research are necessary to verify its efficacy *[114]*. Overall, these outcomes highlight curcumin's possibility as a natural management for psoriasis by regulating inflammatory signaling and controlling excessive keratinocyte growth.

Rottlerin: Rottlerin is a naturally occurring polyphenol extracted from Mallotus philippinensis. It is recognized for its potent anti-inflammatory and antiproliferative effects, suggesting its potential as a treatment for psoriasis *[115]*. In vitro studies demonstrate that rottlerin suppresses keratinocyte overgrowth by blocking NF-κB activation and reducing intracellular ROS accumulation *[116]*. Additionally, it promotes apoptosis in keratinocytes through an autophagy-dependent mechanism while lowering the production of cytokines associated with psoriasis, containing TNF-α, IL-6, IL-17, IL-22, and IL-23 *[117]*.

Further research shows that rottlerin inhibits endothelial cell tube formation, indicating its role in suppressing vascular proliferation, a key factor in psoriasis pathology. In an animal model, rottlerin alleviated psoriasis form lesions by reducing keratinocyte hyperproliferation, inflammatory cell infiltration, and abnormal vascular growth. These findings highlight rottlerin's potential as a therapeutic compound for managing psoriasis by addressing inflammation, oxidative pressure, and keratinocyte dysfunction.

Carotenoid as antipsoriatic:

Lycopene: Lycopene, a carotenoid abundant in tomatoes and red fruits *[118, 119]*, is recognized for its significant anti-inflammatory effects, making it a probable candidate for psoriasis management. Studies have demonstrated that lycopene alleviates psoriasis-like inflammation by reducing keratinocyte production and decreasing immune cell adhesion *[120]*. Both in vitro and in vivo trials have showed lycopene can inhibit intercellular adhesion molecule-1 (ICAM-1), a essential feature in psoriasis development, thereby preventing the infiltration of monocytes and T lymphocytes into inflamed skin *[121]*.

Additionally, the application of lycopene—either topically or orally—has been linked to reduced inflammation and noticeable improvement in psoriasis symptoms. In imiquimod (IMQ)-induced psoriasis models, lycopene treatment led to reduced keratinocyte and monocyte adhesion, indicating its role in modulating immune responses and supporting skin barrier integrity. The compound also exhibits antioxidative effects by neutralizing reactive oxygen species (ROS) that contribute to the inflammatory cycle in psoriasis. *[121]*.

By targeting inflammatory cytokines and adhesion molecules, lycopene may serve as a promising natural agent for psoriasis treatment, offering both symptomatic relief and disease-modifying effects.

Anthraquinones as antipsoriatic:

Emodin: Emodin is a naturally occurring anthraquinone compound present in various medicinal plants, such as *Rheum palmatum*, *Polygonum cuspidatum*, *Polygonum multiflorum*, *Aloe vera*, and *Cassia obtusifolia [122]*, possess various pharmacological properties. It is recognized for its anti-inflammatory, antioxidant, anticancer, antibacterial, and hepatoprotective effects.

Research has demonstrated that emodin can modulate inflammatory responses in psoriasis. In vitro research has shown that treatment with a herbal compound containing emodin at a concentration of 10 μM reduced IL-22-induced keratinocyte proliferation. Additionally, in an imiquimod (IMQ)-induced mice model, topically applied of this natural compound alleviated psoriatic skin inflammation and improved disease symptoms *[123]*. These observation recommend that emodin can serve a valuable therapeutic manager for managing psoriasis by targeting excessive keratinocyte hyperproliferation and inflammatory pathways.

Alkaloidal compound:

Capsaicin

Capsaicin, the bioactive compound in of genus Capsicum, interacts with vanilloid receptors (TRPV1) on sensory neurons, leading to the depletion of component P, a neuropeptide intricate in pain transmission and inflammation. This mechanism reduces vasodilation, angiogenesis, and excessive keratinocyte proliferation, which are hallmark features of psoriasis. Additionally, capsaicin modulates neuropeptide activity, including neuropeptide Y, PGP 9.5, NGF, CGRP, and SP, which are commonly elevated in psoriatic skin and contribute to itch severity. By inhibiting NF-κB and AP-1 signaling, capsaicin suppresses inflammatory responses, leading to a reduction in redness, scaling, and itching *[81]*. Despite its therapeutic potential, its topical application is often limited due to transient burning sensations. However, research, including in vitro studies on HL-60 cells stimulated with TPA, suggests that capsaicin may serve as a promising treatment for psoriasis-related inflammation and neurogenic itch *[80, 124]*.

Table 1: Natural Plant-Derived Compounds with Pharmacological Effects in Psoriasis

Plant source	**Active Compound**	**Pharmacological Effects**	**Mechanism of Action**	***(In Vitro / In vivo)***	
Grapes, Berries, Polygonum cuspidatum	Resveratrol	Antioxidant, anti-inflammatory, anticancer	Downregulates IL-17A, IL-19, IL-23, activates SIRT1, inhibits Akt kinase, reduces keratinocyte proliferation	*In vitro* (NHEK cells), In vivo (psoriasis mouse model)	*[107-109]*
Turmeric	Curcumin	Antioxidant, anti-inflammatory, immunomodulatory	Inhibits NF-κB activation, suppresses TNF-α signaling, reduces keratinocyte proliferation, inhibits PhK action.	*In vitro* (HaCaT cells), In vivo (mice)	*[110, 111, 113]*
Mallotus philippinensis	Rottlerin	Antioxidant, anti-proliferative, anti-inflammatory	Inhibits NF-κB activation, suppresses pro-inflammatory cytokines (TNF-α, IL-6, IL-17, IL-22, IL-23), induces apoptosis	In vitro (HaCaT, NHEKs), *In vivo* (BALB/c mouse model)	*[115-117]*
Tomatoes, Red Fruits	Lycopene	Anti-inflammatory, anti-angiogenic, antioxidant	Inhibits keratinocyte and monocyte adhesion, downregulates ICAM-1, reduces monocytic cell infiltration	*In vitro* (keratinocytes), *In vivo* (IMQ-induced psoriasis mouse model)	*[118, 119, 121]*
Rheum palmatum, Polygonum species, Aloe vera	Emodin	Anti-inflammatory, antioxidant, anti-proliferative	Lowers IL-22-stimulated keratinocyte proliferation, alleviates psoriasis-such as dermatitis	In vitro, *In vivo* (IMQ-induced psoriasis model)	*[122, 123]*
Capsicum spp. (Chili Peppers)	Capsaicin	Anti-inflammatory, neurogenic itch relief, keratinocyte regulation	Interacts with TRPV1 receptors, depletes substance P, inhibits NF-κB & AP-1, modulates neuropeptides (NPY, PGP 9.5, NGF, CGRP, SP), reduces vasodilation, angiogenesis, and keratinocyte proliferation	In vitro (HL-60 cells, TPA-stimulated), In vivo (psoriasis models)	*[80, 81, 124]*

1. CONCLUSIONS:

Psoriasis remains a challenging autoimmune disorder with significant implications for patients' quality of life. The underlying mechanisms involve intricate interactions between immune dysregulation, genetic predisposition, and oxidative stress. While conventional treatments offer symptomatic relief, their continuing use is often restricted because of associated adverse effects. Emerging evidence supports the therapeutic potential of natural composites resultant from medicinal plants, which exhibit anti-inflammatory, antioxidant, and immunomodulatory action. The efficacy of flavonoids, polyphenols, and alkaloids in modulating immune responses and keratinocyte activity suggests an emerging solution for safer psoriasis treatment. Upcoming research should focus on optimizing these natural therapies through clinical trials and exploring their synergistic effects with existing treatments. Integrating phytochemicals into psoriasis management could provide a holistic, effective, and sustainable approach to alleviating disease burden.

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Abbreviations: DC - Dendritic Cells, DNA - Deoxyribonucleic Acid, IFN-γ - Interferon Gamma, IL – Interleukins, MAPK - Mitogen-Activated Protein Kinase NF-κB - Nuclear Factor Kappa B Cells, PUVA - Psoralen plus Ultraviolet A, TNF-α - Tumor Necrosis Factor Alpha.

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