

REVIEW PAPER

NLRP3 Inflammasome in Psoriasis: Role in Disease Pathogenesis, Biomarker Potentiality and Therapeutic Targeting

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ABSTRACT

From an immunological perspective, the term NLRP3 is widely regarded as a critical regulator of immune system dysregulation. The NLRP3 Inflammasome, is basically a complex unit made up of multiple proteins and plays an essential role towards controlling inflammatory signals and the innate immune system. Specifically, pro-inflammatory cytokines. This review provides an overview of the activation process of the NLRP3 inflammasome and the story about the role of this inflammasome in psoriasis and other psoriasis-related immune-system-mediated skin disorders. NLRP3 oligomerisation starts in response to pathogen associated molecular pattern PAMPs and DAMPs, which further triggers caspase-1 and activates caspase-1, which releases mature IL-18 and IL-1 β . The activation of inflammatory reactions is caused by vast intracellular multi-protein signaling complexes called inflammasomes. NLRP3, comes in the group of inflammasomes, has been linked to a number of inflammatory and other autoimmune skin disorders, such as acne, bullous pemphigoid, dermatophytosis, urticaria and other skin problems. Oligomerization of NLRP3 activates caspase-1 by being activated by PAMPs and DAMPs, which kickstarts the process of cleaving and then releasing IL-1 β , IL-18. Focusing on this inflammasome and targeting its downstream signals will yield fresh insights into the creation of future treatment approaches.

Keywords: Psoriasis, NLR Family Pyrin Domain containing - 3, Targeted Molecular Therapies, Tumor Necrosis Factor-alpha, NLRP3 Inhibitors

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1. INTRODUCTION

Psoriasis is an inflammatory immune-mediated condition that has a chronic relapsing-remitting history and accounts for the suffering of 2-3% of people worldwide [1]. The word Psora, which means "itch," and -iasis, which means "action, condition," combine to form the Greek word psoriasis, which means "itching condition" or "being itchy" [2]. According to the World Health Organization (WHO), psoriasis has been tagged as a major non-infectious disease in the year 2014 and highlighted as a serious problem arising due to improper diagnoses, insufficient treatment, and stigmatisation of the condition [3]. Psoriasis, a chronic inflammatory autoimmune illness, is associated with an extraordinarily abnormal hyperproliferation of keratinocytes. Psoriasis has a complicated pathophysiology, and the precise cause is still unknown. But psoriasis is anticipated to be generated by the mixed confluence of genetic, environmental and epigenetic factors. According to recent research, psoriasis is caused by a number of epigenetic

variables, including dysregulated DNA methylation levels, aberrant histone modifications, and microRNA expression [4]. Interleukin-17(IL-17), recognized as a major mediator of proinflammatory immune responses, is primarily released by CD4⁺ T helper 17(Th17) lymphocytes along with several populations of innate lymphoid cells. Reportedly, Atopic dermatitis, pemphigus, and hidradenitis suppurativa, like many such inflammatory skin and autoimmune conditions, have been linked to elevated or dysregulated IL-17A activity. Atopic dermatitis, psoriasis, hidradenitis suppurativa, and systemic sclerosis have been linked to elevated or dysregulated IL-17A activity. Interleukin-23(IL-23) is necessary for stimulating the production of IL-17 through Th17 cell activation. According to new data from clinical trials, an essential direction for targeted treatment of inflammatory diseases is the IL-23/IL-17 axis. Monoclonal antibodies that target IL-17, IL-23 and tumor necrosis factor (TNF) can be a successful treatment option for pityriasis rubra pilaris, psoriasis, systemic sclerosis and other inflammatory diseases [5]. TNF α , IL-17 and IL-23 tactically govern a self-

maintained inflammatory loop created by the interaction between dendritic and T cells in the dermis, which leads to the clinical symptoms of psoriatic plaque [6]. The inflammasome complex mediated by NLRP3, IL-18 and IL-1 β is the most prominent and well recorded contains three domains, namely i) Caspase-1, ii) an apoptosis-associated speck-like protein (ASC) adaptor protein, and Nod-like Receptor Domain (NLR). NLRP3 can be activated by a variety of external inflammatory stimuli, including viruses, bacteria, and other PAMPs and DAMPs [7]. In humans, the NLRP3 gene encodes cryopyrin, a member of the NOD-like receptor family commonly referred to as NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3) located on chromosome 1. This protein is predominantly found in macrophages and functions as a key intracellular sensor in innate immunity. Upon activation, NLRP3 associates with the adaptor molecule ASC and procaspase-1 to assemble the NLRP3-dependent inflammasome complex. IL-18 and IL-1 β are inactive precursor forms that are eventually transformed into their physiologically active cytokines by the action of caspase-1 [8]. Also, several studies have indicated that psoriasis susceptibility is linked to polymorphisms in NLRP1, NLRP3, and CARD8 [9]. Inflammasome activation is considered one of the main cascades that the host defense system uses to combat many infections. The activation of this inflammasome is frequently stimulated by ion fluxes. These consist of Cl⁻ efflux, Ca²⁺ flow, and K⁺ efflux, of which K⁺ efflux is an essential upstream event (Swanson et al. 2021). Initially, it was found that mature IL-1 β production was enhanced by ATP-mediated P2X purinoceptor 7 (P2X7) via K⁺ efflux. Moreover, it might make it easier to connect with the adaptor ASC protein, which would encourage caspase-1 and caspase-11 activation. The processing and secretion of inflammatory cytokines, such as IL-18 and IL-1 β are significantly influenced by these events (Smith et al., 2024). These events have an important impact on IL-1 β and IL-18 processing and their secretion. On the other hand, high extracellular potassium (K⁺) levels are reported to suppress NLRP3 inflammasome activation [10]. However, novel research findings indicates that the pathophysiology of a number of diseases with low-grade inflammatory states as a backdrop also depends on the activation of inflammasomes. NLRP3 assembly is turned on with the help of a wide range of endogenous and exogenous activators, such as microbial signals, toxins, crystalline materials, peptide aggregates, and extracellular ATP produced by dying cells. It is reported that NLRP3 is part of inflammasomes and is involved in CMS pathogenesis. It may help in the recruitment of the adaptor protein and subsequently activate both caspase-11 and 1 respectively, all of which are critical processes in the maturation and release of the pro-forms of IL-18 and IL-1 β ; it can also trigger cardiomyocyte apoptosis, activate cardiac

fibroblasts, and induce cardiac myopathies, trauma etc. [11]. Another mechanism that can be used to downregulate NLRP3 inflammasome activation is Adaptive Immunity. It has been demonstrated that stimulating macrophages with NLRP3 agonists while activated T cells are present. These cells try to inhibit NLRP3 inflammasome activation. It is interesting to note that after experimentally inhibiting the NLRP1 inflammasome, neither the activation of the NLRP4 inflammasome nor noncaspase-1-dependent cytokines is found to be affected. Macrophages are essential cells of the innate immunity and are involved in the pathophysiology of post-ischemic inflammation and several chronic inflammatory disorders. Numerous proinflammatory cytokines and chemokines gets secreted by activated macrophages, with IL-1 β being one of the most effective in causing inflammation and accelerating the course of disease. The inflammasome pathway regulates both the maturation and release of IL-1 β and IL-18 [8]. Large intracellular protein complexes termed as inflammasomes attract and activate the caspase-1 protease, which cleaves pro-IL-18 and IL-1 β into their released and physiologically active forms to create inflammation in the body [12].

2. ROLE OF NLRP3 INFLAMMASOME IN PATHOGENESIS

Structurally the NLRP3 mediated inflammasome complex is consisted of 3 main parts: NLRP3, which detects danger signals and along with acts to attract several molecules placed downstream; caspase-1, which causes the cytokines IL-18 and IL-1 β and o mature and processes gasdermin D to stimulate cytokine release and trigger pyroptosis; and ASC; which acts as a link in between caspase-1 and NLRP3 protein [10]. The inflammatory caspases, which include caspase-1, are a subset of caspases that are activated by supramolecular signaling complexes called inflammasomes. When triggered by microbial and damage-related cues, inflammasomes come together to trigger the first line of defense for the host by causing pyroptotic cell death and the proteolytic maturation of IL1 β and IL18. In order to trigger Inflammasome assembly the activation of an upstream sensor, a downstream effector, and, often, an adaptor molecule like the ASC protein is a necessary requirement. Inflammasomes can be classified as either ASC-dependent or ASC-independent based on whether ASC is necessary [9]. There is numerous recently published literature pointing out the relationship between certain metabolites and the NLRP3 inflammasome. Also, the evidence gathered from several studies supports the significance of AIM2 and NLRP3 in the pathophysiology of psoriasis and its systemic symptoms, as well as the substantial upregulation of inflammasome genes in psoriatic epidermis. Additionally, trauma, skin damage, and UV Metabolites cause damage to the skin. In this case, the inflammasome pathway gets activated and involves

releasing Neutrophils which attack Skin cell [4] (as illustrated in figure 1).

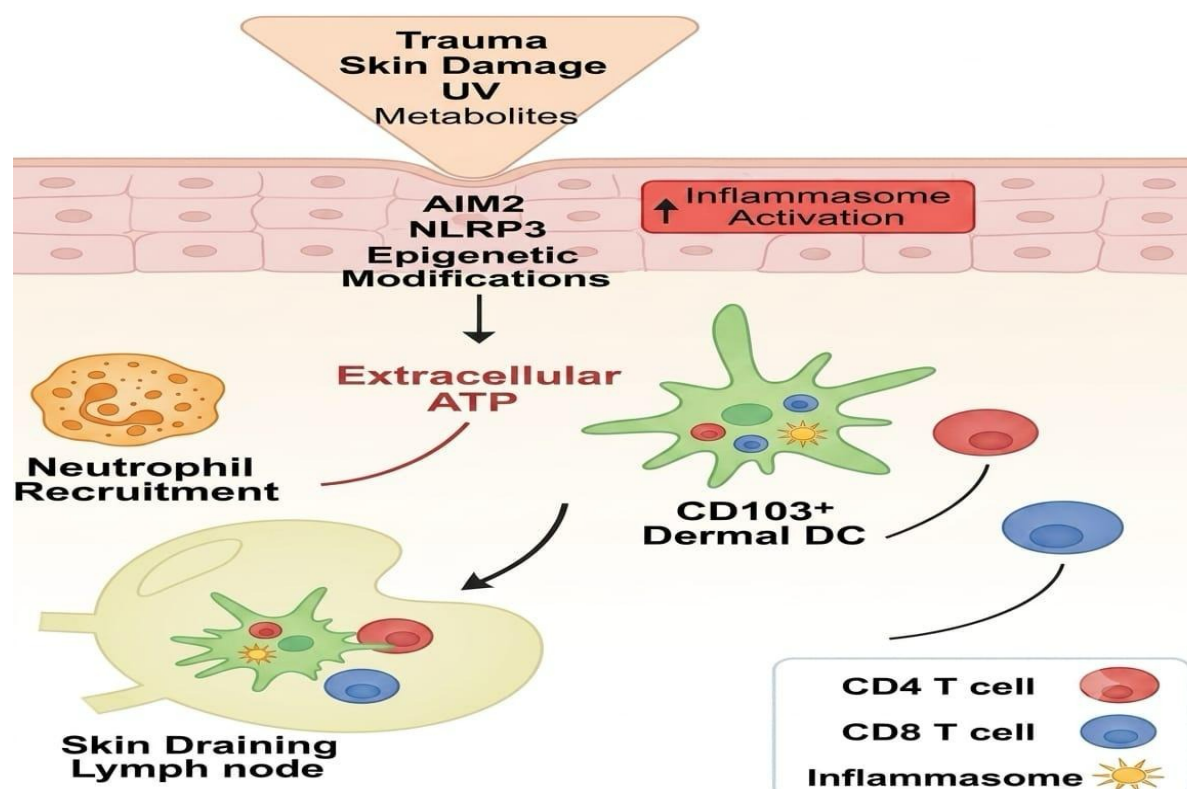


Figure 1: Trauma, ultraviolet (UV) exposure, skin damage, and altered metabolites contribute to activation of AIM2 and NLRP3 inflammasomes in the skin. Inflammasome activation promotes the release of extracellular ATP and enhances innate immune signaling. These signals facilitate neutrophil recruitment and activation of CD103⁺ dermal dendritic cells (DCs). Activated immune cells migrate toward the skin-draining lymph nodes and promote CD4⁺ and CD8⁺ T-cell responses. This interconnected inflammatory network may contribute to sustained cutaneous inflammation and psoriasis pathogenesis.

Reportedly, any chemicals, such as crystalline substances or other particulate materials, can activate the NLRP3 inflammasome. Accordingly, scientists demonstrated that cholesterol crystals may trigger the inflammasome pathway and further induce inflammation. This discovery opened the door for additional studies that show a link between NLRP3-dependent inflammasome biomarker activation and the development of metabolic disorders such as cardiometabolic syndrome [13]. Two signals, namely (Signal 1) i) priming and (Signal 2) ii) protein complex formation, are the most important conditions for NLRP3 inflammasome activation. Pattern recognition receptor signaling, such as TNF signaling or TLR4 activation, initiates the priming process. This, in turn, transcriptionally activates NLRP3, pro-IL-1 β , and IL-18 through pathways that are dependent on nuclear factor- κ B (NF- κ B). However, new studies indicate that the priming process of NLRP3 inflammasome activation is complex, including several protein binding partners and combining transcriptional and posttranslational pathways. A

variety of PAMPs and DAMPs, including extracellular ATP, toxins capable of forming membrane pores, RNA-based viral agents, and particulate matter or cellular debris, cause the activation signal (Signal 2). Signal 2 activation involves a variety of molecular or cellular processes, such as lysosomal damage, ion flow (K⁺/Cl⁻ efflux and Ca²⁺ influx), mitochondrial malfunction, and the formation of reactive oxygen species (ROS). Both microbial and sterilized inflammatory stimuli can initiate Signals 1 and 2; however, the kinetics and amplitude of microbial signals differ from those of sterilized signals [14]. Inflammasomes are platforms that need to be assembled in response to encounter diverse DAMPs and PAMPs. Inflammasome sensors (with or without ASC assistance) trigger caspase-1 and other inflammatory caspases upon activation, which cleave precursor form of IL-1 β , IL-18 and simultaneously cleaving gasdermin D, resulting in mature cytokine release and pyroptosis. In response to the events like cell death, pyroptosis allows intracellular pathogen niche disruption and release of

intracellular content, which triggers pro-inflammatory reactions in nearby cells. A powerful pro-inflammatory regulator, IL-1 β promotes T-cell

proliferation, neutrophil recruitment, and macrophage activation [15] (as illustrated in figure 2).

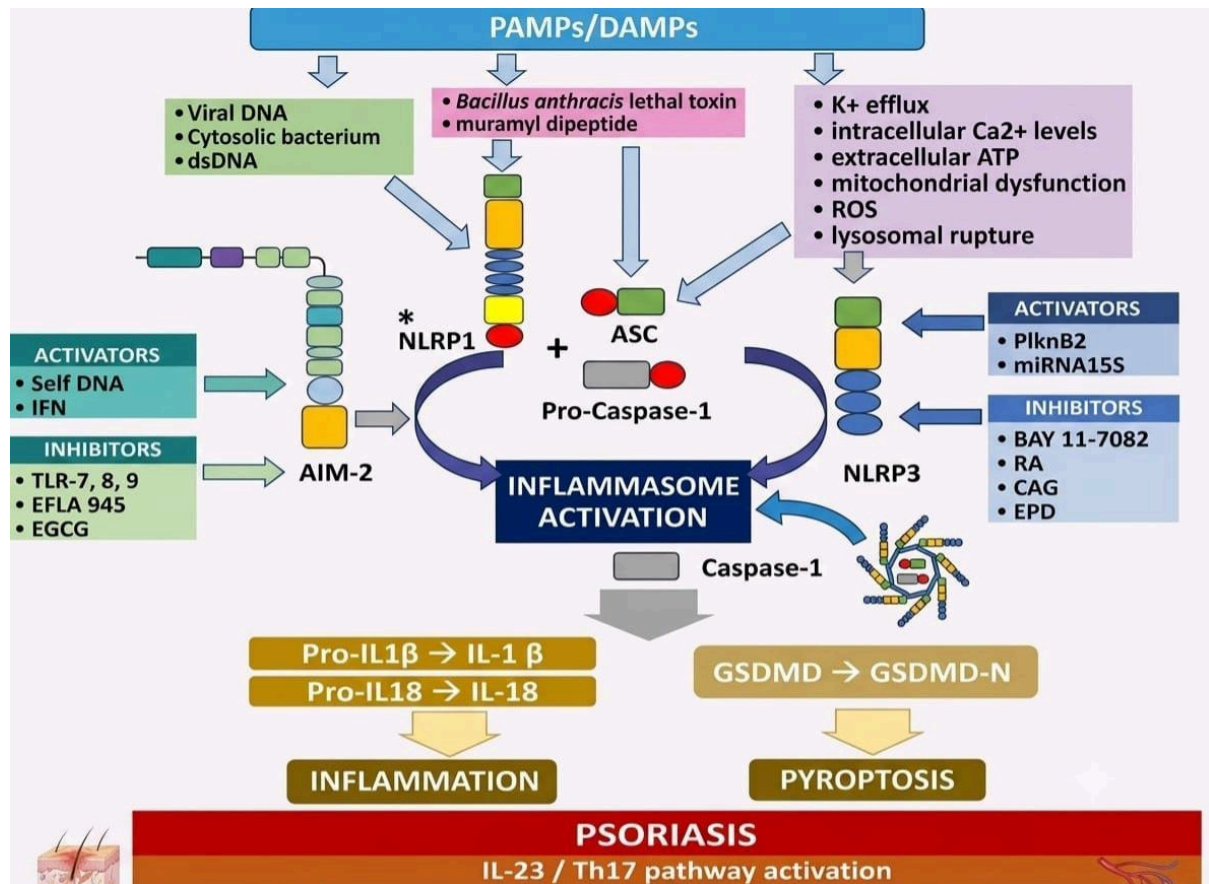


Figure 2 : Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) activate absent in melanoma (AIM2) and NLRP3 inflammasomes through distinct upstream signals. AIM2 primarily senses cytosolic DNA, whereas NLRP3 responds to diverse cellular stress signals, including K⁺ efflux, mitochondrial dysfunction, ROS, and lysosomal damage. Inflammasome assembly recruits ASC and pro-caspase-1, resulting in caspase-1 activation. Activated caspase-1 promotes maturation of IL-1 β and IL-18 and cleavage of gasdermin D (GSDMD). Consequently, inflammatory signalling and pyroptotic cell death contribute to IL-23/Th17 pathway activation, inflammatory-cell infiltration, and keratinocyte hyperproliferation characteristic of psoriasis.

3. ROLE IN PSORIASIS PATHOGENESIS

Keratinocytes, the number of immune cells and the rest of the skin cells, like endothelial cells, interact dynamically in psoriasis, which is considered a complicated health condition. Epidermal hyperplasia associated with extensive dermal cell infiltration by various immune cells, such as dendritic cells and T lymphocytes, is caused by aberrant proliferation and keratinocyte differentiation. The most significant characteristics of psoriasis are the increased density of dermal capillaries and the overproduction of a number of inflammatory chemokines and cytokines. An inflammatory milieu, mostly mediated by IL-17, is largely dependent on the interaction that takes place between keratinocytes and immune infiltrating cells illustrated in the disease itself [7]. Psoriasis

susceptibility has been linked to a genetic component linked to the inflammasome. The inflammasome multiprotein complex, which is involved in the synthesis of IL-18 and IL-1 β , two inflammatory cytokines observed in Psoriasis pathogenesis, may be activated during the pathogenesis of Psoriasis, according to certain data. Interaction between the inflammasome receptor and the adaptor ASC protein containing a caspase-recruitment domain facilitates the assembly of the inflammasome components. The inactive precursor of caspase-1 is subsequently recruited, and the effector caspase is activated by the help of a proteolysis-mediated cleavage process. These precursor forms of IL-18 and IL-1 β are subsequently cleaved by activated caspase-1 to provide active versions of these pro-inflammatory

cytokines. It's interesting to note that polymorphisms of the NLRP1 inflammasome complex have also been linked to a higher risk of developing psoriasis, as found in recent research [16]. Numerous studies suggest that the pathogenic mechanism of psoriasis may involve IL-18. Actually, the information that is now available indicates that this cytokine plays a crucial function in stimulating the proliferation of keratinocytes and acting as a strong chemoattractant for neutrophils and T lymphocytes [17]. IL-17 is recognized as a major inflammatory cytokine chiefly synthesized by CD4⁺ Th17 lymphocytes as well as certain populations of innate lymphoid cells. Dysregulated IL-17 signalling has been implicated in several inflammatory and autoimmune skin disorders,

including psoriasis, hidradenitis suppurativa, atopic dermatitis and systemic sclerosis among the inflammatory illnesses linked to IL-17A and different PAMPs and DAMPs. Through Th17 cell activation, IL-23 is essential for promoting the synthesis of IL-17. An essential avenue for targeted treatment of inflammatory illnesses is the IL-23/IL-17 axis. Some clinical trials indicate that through monoclonal antibodies designed against IL-23, IL-17, and tumor necrosis factor, psoriasis can effectively be cured. Hidradenitis suppurativa, psoriasis and systemic sclerosis [5] (as illustrated in figure 3). According to Krajewski et al., Psoriasis is linked to a polymorphism in the NLRP3 (rs10754558) gene [18].

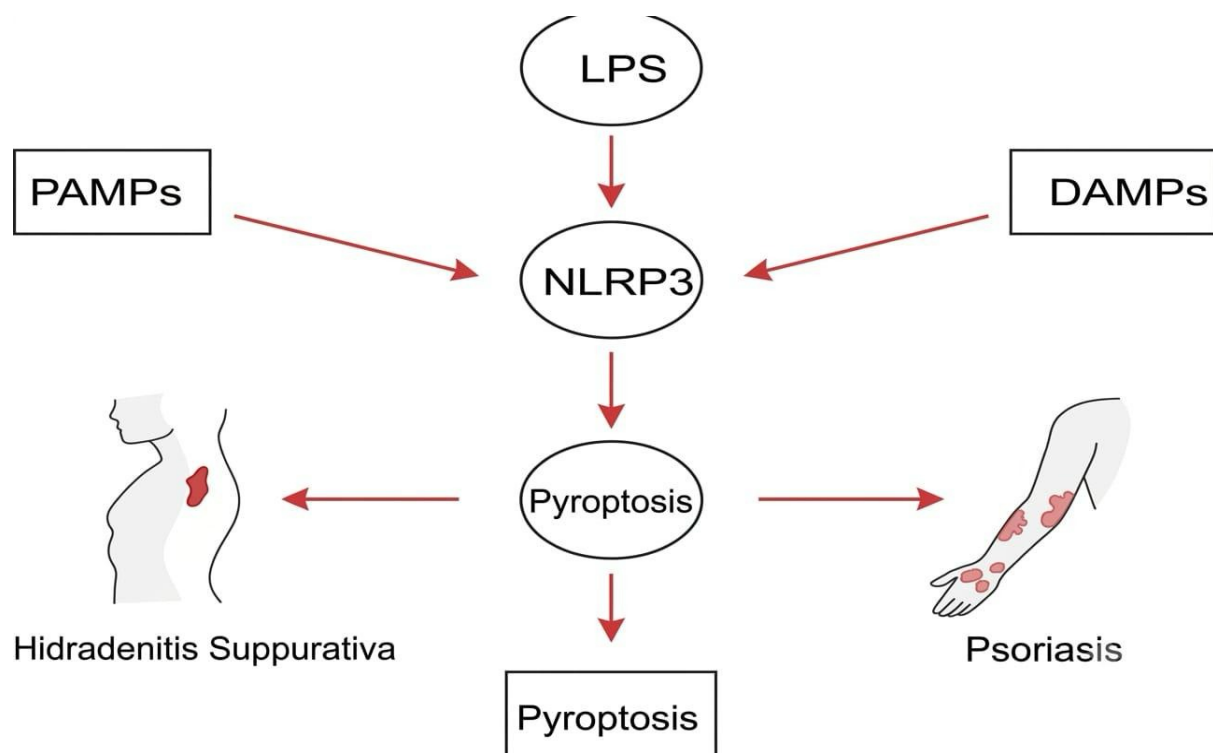


Figure 3: PAMPs and DAMPs, including microbial and endogenous danger signals, converge on activation of the NLRP3 inflammasome. NLRP3 activation promotes assembly of the inflammasome complex and downstream inflammatory caspase signalling. This pathway culminates in pyroptosis, an inflammatory form of programmed cell death associated with the release of intracellular inflammatory mediators. NLRP3-driven pyroptotic responses can amplify local tissue inflammation and immune-cell recruitment. Dysregulated NLRP3–pyroptosis signalling has been implicated in chronic inflammatory skin disorders, including psoriasis and hidradenitis suppurativa.

4. NLRP3 INFLAMMASOME COMPONENTS AS BIOMARKERS IN PSORIASIS

After being activated, the NLRP3-controlled inflammasome may result in the formation of IL-18 and IL-1 β . IL-18 stimulates the synthesis of IFN- γ , which is basically a co-stimulatory cytokine that helps induce adaptive immunity. Increased IL-1 β signalling encourages the generation of IL-23, while IL-1 β induces Th17 cells to generate IL-17A. Th17 cells are among the many cells that IL-23 can affect. $\gamma\delta$ T cells

can generate elevated IL-17 levels, which create an initial positive feedback loop to sustain psoriasis patients' skin lesions. Co-regulation of chemokine IL-17 and IFN- γ receptor expression can lead to dysregulation of chemokine signalling, which in turn causes keratinocyte hyperproliferation and infiltration of immune cells in the injured skin [11]. Similarly, in psoriasis, IL-23/IL-23R/IL-17 promotes the synthesis of cytokines and the progression of inflammation [19]. After the discovery of the biological role of the IL 23/-17 axis, IL-23 and IL-17 have been found to

play a significant role in the pathophysiology of a number of immune-mediated disorders. Th17 levels are higher in psoriatic skin lesions than in healthy people, and IL-17, IL-23, IL-22, and IL-23R levels are reported to be higher in psoriatic skin plaques than in non-lesional skin and healthy biopsies [20]. According to the study published in 2023, lowering the baseline level of IL-6 may help encourage a response towards neutralizing TNF- α . Researchers identified some useful outcomes for IL-6 in individuals treated with adalimumab. Since IL-6 is essential for Th17 cell development, a low IL-6 concentration may be associated with a comparatively low Th17 cell count. Rheumatoid arthritis patients have been shown a reduced therapeutic response to TNF- α inhibitor treatment in cases of higher basal levels of circulating Th17. An increased baseline proportion of circulating Th17 cells has been found linked with a reduced therapeutic response in patients with rheumatoid arthritis. This paper has also meticulously explained that the Systemic Inflammation Index (Neutrophils $\times$ Platelets) /Lymphocytes may be utilized as a predictive biomarker to see how well a patient will respond to biologic therapy. Notably, bio-naïve responders showed lower baseline levels of NLR and IL-6 than bio-naïve non-responders against TNF- α inhibitors [20]. Also, Mast cells play a well-known function in inflammation; tryptase is one of the inflammatory mediators that can be released when mast cells in the skin and joints are activated [21].

5. Therapeutic Targeting of NLRP3 Inflammasome in Psoriasis

In order to treat comorbid disorders, a number of therapeutic medicines that target these cytokines and/or their receptors have now been established. In psoriasis, IL-17 and IL-12/-23 targeted therapies seem to be especially beneficial, and encouraging findings are also being observed in spondyloarthropathies. The adverse-event rates of these medicines are comparable to those of other biologic therapy programs, suggesting that they are generally well tolerated. Blocking IL-23 and inhibiting IL-17 can help treat deadly diseases like psoriasis, ankylosing spondylitis, Crohn's disease, etc [22]. It is an established fact that there is a significant hereditary component linked to psoriasis. Human Leukocyte Antigen (HLA) and non-HLA loci are among the important single nucleotide polymorphisms (SNPs) linked to this pathophysiology. TNF promoter area polymorphisms are important for the outcome of therapy response. Response to TNFi treatment has been linked to the TNFAIP3 gene or A20. TNFAIP3 was initially identified as a TNF alpha negative feedback inhibitor that stops the NF κ B transcription factor from activating. TNFAIP3 gene expression is also induced by IL-17. It's interesting to note that A20 interacts with IL-17 in a different way than other routes, and further study is required to see whether polymorphisms at A20 affect how well TNFi-like IL-17 inhibitors

work. A recent study conducted found that IL-17i and its effect on inflammatory indicators were linked with proteomic sources. Secukinumab medication reduced the ESR of CRP Protein and Matrix Metalloproteinase -3 production in clinical responders in a small group of Psoriatic Arthritis patients. The MMP-3, IL-6, IL-17A, and CC- motif Chemokine ligand 20 mRNA expression was significantly reduced [23].

6. DIRECT INHIBITORS OF NLRP3 PROTEIN

6.1 MCC950

One of the most effective and specific inhibitors of NLRP3-mediated inflammasome is a substance called MCC950, which contains diarylsulfonylurea. MCC950 is being developed carefully as a therapy for problems driven by NLRP3. MCC950 was first experimentally proven to prevent caspase-1 from maturing into IL-1 β . Later, NLRP3 Inflammasome complex can be activated through Canonical and Non-Canonical pathways. Coll et al. reported that MCC950 can act as a blocker of both of these pathways and can inhibit IL-1 β production in human and mouse macrophages by preventing ASC oligomerization. The activation of the NLRP1, NLRC4, and AIM2 inflammasomes was notably unaffected by MCC950. According to a different recent study, MCC950 inhibits hydrolysis of ATP molecules and the production of NLRP3 inflammasomes by directly binding to the Walker B motif of the NACHT domain on NLRP3 [24]. Recently, a study demonstrated that an interaction takes place between MCC950 and the NACHT domain of wild-type NLRP3, which can be detected using iBody technology and photoaffinity labelling. The majority of cryopyrin associated periodic syndrome (CAPS) -related NLRP3 mutations showed reduced binding, and MCC950 did not prevent the NLRP3-induced inflammatory disease in two CAPS animal models. MCC950 may only be useful in conditions involving inflammation caused by the wild-type protein of the NLRP3 gene. These conditions may be caused by NLRP3 mutations linked to CAPS [25].

6.2 CY-09

CY-09 prevents ATPase activity and oligomerization, hence inhibiting the activation of the inflammasome by competitively attaching itself to NLRP3's ATP-binding site (Jiang et al. 2017). It has been observed that CY-09 efficiently inhibits tissue damage and inflammatory responses mediated by NLRP3. CY-09 mitigates intestinal damage and downregulates the proinflammatory cytokine expression such as TNF- α , IL-18, and IL-1 β in II/RI mice [26]. A potent and direct NLRP3 inhibitor was discovered that significantly reduced the NLRP3 inflammasome both ex-vivo in human cells and in-vivo in mouse models. CY-09, a structural derivative of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)172

(C172), inhibits the CFTR chloride channel. CY-09, a structural derivative of (CFTR)172 (C172), inhibits the (CFTR) chloride channel [27]. BMDMs primed with LPS, CY-09 inhibited the maturation of caspase-1 and subsequent release of IL-1 β in a dose-dependent manner by ATP, monosodium urate and nigericin. Signal 1 and NLRP3 based post-translational modification are not necessary for its inhibitory action. It interacts directly with the NLRP3 Walker mechanistically, a motif that prevents NLRP3 from binding to ATP, but it has no effect on NLRP1, RIG-1, NOD2 and NLRC4 [28]. According to recent researches, CY-09, a tiny and very selective agent which works as an inhibitor of NLRP3 and does not depend on NF- κ B signaling, exhibits therapeutic benefits in metabolic and inflammatory disorders such as non-alcoholic fatty liver syndrome & type 2 diabetes [29].

6.3 OLT1177

OLT1177, also known as Dapansultrile, is a β -sulfonyl nitrile molecule that specifically inhibits the activity of NLRP3 ATPase134,135 (as shown in Table 1). In experimental ischemia–reperfusion damage mice, OLT1177 administration decreased the size of the infarct80. Mice with severe ischemic cardiomyopathy have also been exposed to OLT1177. Upon administration of OLT1177 to mice for one week, the outcome showed permanent coronary artery ligation; diastolic function improved and cardiac reserve rose in comparison to control mice13 [30]. Olatec Therapeutics is developing OLT1177 (also known as dapansultrile) as an NLRP3 blocker. It has completed a Phase IB trial (NCT03534297) with no significant side effects recorded, showing improvement in patients with serious heart ailments who have a reduced left ventricular ejection fraction [31]. Apart from this, several natural compounds have been proven to show inhibitory effects against the action of this inflammasome (as illustrated in figure 4).

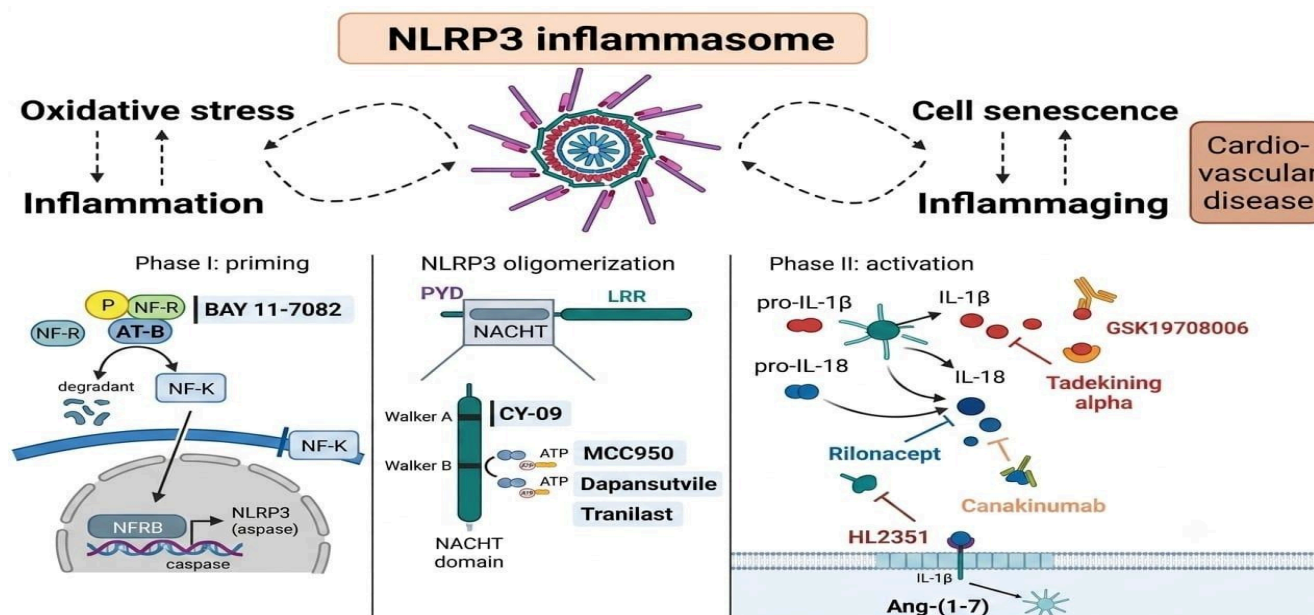


Figure 4: Oxidative stress and cellular senescence represent important upstream stimuli that promote NLRP3 inflammasome activation and contribute to chronic inflammation and inflammaging. NLRP3 inflammasome activation involves distinct priming and activation phases, leading to transcriptional induction and subsequent assembly of the inflammasome complex. NLRP3 oligomerization facilitates recruitment of downstream signaling components and promotes processing of pro-inflammatory cytokines. Activation of the inflammasome results in maturation and release of IL-1 β and IL-18, thereby amplifying inflammatory responses. The figure also highlights pharmacological strategies targeting different stages of NLRP3 signaling, including inhibitors of priming, oligomerization, and downstream IL-1 β /IL-18 pathways. Dysregulated NLRP3 activity may contribute to inflammaging and age-associated disorders, including cardiovascular disease, underscoring its potential as a therapeutic target.

7. INDIRECT INHIBITORS

7.1 Curcumin

The main active ingredient present in turmeric, curcumin, was traditionally used as a spice and food color agent. Curcumin possesses some anti-

inflammatory properties by preventing the infiltration of macrophages and the NF- κ B signaling in adipose tissue that is brought on by inflammatory agents. In addition, curcumin has been shown to suppress the expression of several proinflammatory adipokines, including TNF- α , monocyte chemoattractant protein-

1(MCP-1) and plasminogen activator inhibitor-1. By downregulating the production of nitric oxide, prostaglandin E2 and TNF- α , and inhibiting the phosphorylation of p38, ERK, Akt, and MAPKs, along with the of NF- κ B activity, curcumin induced activity which is anti-inflammatory in nature in lipoteichoic acid-induced microglial cells [32]. It has been established that curcumin, particularly through its anti-IL-22 action on Keratinocyte proliferation, can decrease NLRP3 inflammatory bodies, hence reducing psoriasis-like skin lesions in a mouse model. By lowering NLRP3 expression, curcumin can not only lessen the inflammatory response caused by IL-22 and IL-18, but it can also potently prevent IL-22-induced STAT3 phosphorylation. It was found that Curcumin suppressed phosphorylation in normal cells almost entirely; it inhibited phosphorylation of STAT3 caused by IL-22 by up to 95.6% and inhibited phosphorylation of IL-22 and IL-18 by roughly 47% [33].

7.2 Resveratrol

In a number of studies, resveratrol and other naturally occurring immunosuppressive compounds (stilbenoids, including piceatannol, pterostilbene, and gnetin) have been discussed as an inhibitor of NLRP3 Inflammasome. These acidic and amphiphilic non-nitrogen polyphenols target protein kinase B (PKB/Akt), 5-lipoxygenase (5-LOX), and COX-2. Zhou et al. evaluated resveratrol's inflammation-restricting properties by experimenting on an acute pharyngitis rabbit model. Additionally, Wang et al. demonstrated the potent analgesic and anti-inflammatory properties of resveratrol in a mouse model in which xylene was used to generate ear oedema. Resveratrol's anti-inflammatory properties have also been shown in research on intestinal disease and neurological problems [34]. Resveratrol has been identified as a lowering agent of proinflammatory mediator levels in a rat model of Crohn's disease, including TNF- α , TGF- β 1, IL-1 β and IL-6. Additionally, curcumin, resveratrol and simvastatin reduced the production of TNF- α , IL-23p19, MCP-1 and IL-6 after peroral infection with *Toxoplasma gondii* in a mouse model of which can be acted as a mimic of hyper-acute Th1-type ileitis [35]. When plants are exposed to stressors like UV light or infection they produce resveratrol, a phytoalexin, through the shikimate-derived phenylpropanoid pathway. Other related stilbenoids and derivatives, including oxyresveratrol, its dimer ϵ -viniferin, and its

metabolite piceatannol, have also shown notable bioactivity in skin models, addressing disorders including psoriasis and atopic dermatitis. Because it can activate several important signaling pathways, Resveratrol has therapeutic promise. Reducing oxidative stress through antioxidant pathways (e.g., NRF2), reducing inflammation by blocking important regulators such as NF- κ B and regulating cell division and death through caspase-dependent pathways and sirtuin activation (e.g., SIRT1) are its main strategies [36].

7.3 Quercetin –There are certain rich sources of quercetin, a flavanol and secondary metabolite of plants like Apples, berries, onion, grapevines, broccoli and capers. Quercetin scavenges reactive oxygen and nitrogen species and targets important pro-inflammatory signaling cascades, including MAPK, STAT1 and NF- κ B. Inflammatory sarcoidosis has been hypothesized to be caused by low antioxidant levels and oxidative stress. In patients with sarcoidosis who took part in a double-blind research, quercetin (15 mg daily) was found to decrease inflammation and increase antioxidant defense through rising total plasma antioxidant capacity [37]. Numerous investigations have revealed the anti-inflammatory properties of Quercetin which has been typified by the modulation of numerous different signaling routes, such as the NRF-2 route, the NF- κ B and the MAPK [38]. Through the regulation of several signaling pathways (NF- κ B, MAPK, SIRT1, NRF2, etc.), Quercetin prevents the initiation of NLRP3 driven inflammasome activation and enhances the degree of the disease severity. Numerous studies have demonstrated the effectiveness of quercetin's anti-inflammatory properties at dosages that are essentially consistent. However, the safety of treating it at large doses (100 or 150 mg/kg/day) is unknown [39]. Moreover, an experimentally conducted study in the year 2025 stated that Six polyphenols compounds were found to successfully inhibit keratinocyte hyperproliferation, a pathognomonic hallmark of psoriatic lesions, through different but complementary methods. The strongest anti-proliferative effects were shown by quercetin, in which animal models were found having increased orthokeratotic areas while dramatically decreasing epidermal thickness. This double effect implies quercetin not only prevents aberrant proliferation but also encourages normal differentiation processes, which are necessary for a healthy skin structure [40].

Table 1: Compounds with NLRP3 Inflammasome inhibition property and their mechanism of action towards inhibiting the NLRP3 Inflammasome, potency and their effect on related pathways.

Name of Inhibitors	Mechanism of Action	Inhibitor Type	Potency (IC50)	Cell Type/Tissue s Studied	Effect on Related Pathways	References

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Direct NLRP3 Inhibitors	Experimental compounds such as MCC950, CY-09, and OLT1177 have demonstrated suppression of inflammasome activation.	Offer targeted intervention at an early stage of the inflammatory cascade.	Offer targeted intervention at an early stage of the inflammatory cascade.	Mouse Bone marrow-derived macrophages (BMDMs)	Clinical trials evaluating efficacy in psoriasis patients.	[12]
MCC950	Inhibiting apoptosis associated speck-like Protein (ASC) oligomerization, suppressing canonical and Non-canonical NLRP3 Inflammasome	Direct NLRP3 binder	~7.5 Nm	Bone marrow-derived macrophages (BMDMs)	Blocks downstream Caspase-1 & IL-1 β maturation	[50]
CY-09	Inhibits NLRP3 ATPase activity, blocks NLRP3 Inflammasome activation	Direct NLRP3 ATPase inhibitor	~ 10 μ M	Macrophages, animal models	Blocks ATP binding; reduces pyroptosis	[30]
Resveratrol	Inhibits the expression of NLRP3 Inflammasome. IL-1, IL6, TNF- α expression level inhibited	Indirect (activates SIRT1)	Effective at 10-100 μ M	Neurons, multiple organs	Reduces oxidative stress; NF- κ B inhibition	[51]
OLT1177	Inhibits NLRP3 blocks ATPase activity which blocks NLRP3 Inflammasome activation	Direct NLRP3 ATPase inhibitor	~ 1.1 μ M	Human PBMCs, clinical samples	Reduces IL-1 β in autoimmune diseases; safe in humans	[30]
Quercetin	Inhibits NLRP3 Inflammasome expression in kidney tissues of Male sprague Dawley rats	Indirect	Effective at 20-50 μ M	Male Sprague Dawley rat kidney	Reduces renal IL-1 β and inflammasome expression	[51]

8. PHYTOCHEMICALS AS A CLINICAL PRACTICE AGAINST INFLAMMATORY PATHWAYS IN TREATING OTHER INFLAMMATORY DISEASES

The development of anti-inflammatory plant extracts as a clinical practice was made possible by developing awareness about traditional medicinal plants as a therapeutic target. Synovial inflammation is decreased by a polyherbal formulation that contains triphala extract, ashwagandharishta, balarishta, and dashmoolarishta. Withania somnifera L root extracts were investigated in a rat model on Inflammatory Bowel Disease by Pawar et al. (2011). In 2008,

Rodrigues Silva and his team have investigated the anti-inflammatory qualities of Piper ovatum Vahl leaves. Fermented Asava and Arishta compositions are already described in Ayurveda. These formulations are nothing but the plant extracts those have undergone microbial fermentation, which permits biological change and may result in the production of novel fermentative phytochemical compounds with enhanced bioavailability and anti-inflammatory properties. In some studies Eulophia ochreata L. tubers extract had anti-inflammatory benefits on rats given carrageenan [41,42].

9. NLRP3 INFLAMMASOME AND PSORIASIS COMORBIDITIES

Psoriasis is now considered to be a systemic inflammatory disease due to the growing epidemiologic and fundamental scientific evidence. The pathophysiology of psoriasis's systemic inflammation serves as the foundation for the development of extracutaneous comorbid disorders and explains why psoriasis treatments, such as biologics and conventional systematic drugs, enhance the condition's extracutaneous comorbidities. Bullous disease, asthma, and periodontitis are examples of more systematic diseases that are found as fresh comorbidities of psoriasis, in addition to the major comorbidities of psoriasis, CAD and CKD. This helps to understand psoriasis and the link of it with comorbid diseases [43]. The study of psoriasis has recently focused on mental health because it not only negatively affects a patient's psychological well-being, which can result in a variety of psycho-emotional issues, but it also significantly alters the nervous system through inflammation caused by immune dysregulation. There is an epidemiological evidence that psoriasis treatment improves comorbidities, and bidirectional connections between psoriasis and extracutaneous comorbidities, including depression, vitiligo, celiac disease, and chronic kidney disease. According to last 5 years epidemiological data more systemic disorders have been recognized as extracutaneous comorbidities of psoriasis [44,45].

10. CHALLENGES AND FUTURE DIRECTIONS

Some studies suggest that in case of TNF- α , it doesn't absolutely require priming signal to activate the NLRP3 inflammasome. It has also been discovered that TNF- α signals via the TNFR-caspase-8-caspase-1 alternative route of inflammasome activation, which operates without pyroptosis. The result of TNF neutralizing therapy came out in the form of normalized caspase-1 reactivity and normalized plasma IL-18 and IL-1 β level [46]. While on the other aspects, patients who were treated with methotrexate showed persistently elevated caspase-1 reactivity. Thus it can be demonstrated that systemic inflammation may be exacerbated by TNF-mediated activation of NLRP3 inflammasomes in psoriasis patients. These kinds of heterogeneity has been observed in different patients in terms of treatment outcome during NLRP3 Inflammasome mediated psoriasis treatment [47,48]. Many studies have found biomarkers of nonspecific generalized inflammation, such as acute phase reactants like CRP, which may not be unique to prevalent psoriasis comorbidities because they can be raised in a number of inflammatory disorders [49,50]. The potential of sophisticated analytical AI techniques such as Variational Graph Autoencoders (VGAEs) and K-means clustering has been emphasized in

comprehending pyroptosis associated with the NLRP3 inflammasome in periodontal disease. By identifying gene expression profiles, K-means clustering makes individualized treatment possible. Though it has to be improved for better efficiency and interpretability, the VGAE model achieves remarkable accuracy and precision [51]. Future studies should investigate hybrid methodologies, integrate domain-specific knowledge, and refine initialization strategies to improve the analytical capabilities of the VGAE model and K-means clustering in assessing gene expression data and reconstructing graph topologies. This may result in novel treatment approaches that focus on the underlying causes of the disease, enhancing patient outcomes in cases with NLRP3 based periodontal inflammation [52,53]. However, the nonspecific targeting of catalytically significant cysteine residues by the currently available inflammasome inhibitors results in off-target actions and raises concerns about cytotoxicity [54]. Most of the researchers think that a thorough structural understanding of NLRP3 and the development of more "druglike" target covalent modifiers through the application of a structure-based drug design method will be key to the medicinal chemistry of effective medications in the future [55]. High efficacy, selectivity, and a prolonged duration of action are anticipated from NLRP3 inhibitors that covalently target accessible, appropriately positioned, and unconserved nucleophiles. The unexpected Cys-8 and Cys108 residues were found to be highly conserved across species in the crystallographically resolved structure of human NLRP3 Pyrin domain. The formation of a disulfide bond between these two cysteine residues may play a significant role in controlling NLRP3 activation through ROS and redox potential [56]. Some studies in this field tries to raise the prospect that NLRP3 inflammasome activation could be avoided by specifically targeting important, unconserved residues and regions. This raises a similar question: will the redox microenvironment have an impact on small-molecule inflammasome inhibitors that are cysteine modifiers? In fact, glutathione and other molecules linked to redox regulation may potentially react with cysteine modifying agents [57]. Moreover, It has been noticed that compound 17's inhibitory effect was much diminished when the amount of free cellular glutathione was raised. Thus, it is crucial to take into account how inflammasome inhibitors affect the cell's redox state in addition to their capacity to restrict the processing and release of IL-1 β [58].

11. CONCLUSION

NLRP3 playing a significant role in imparting a set of inflammatory diseases by limiting the capacity of immune responses or controlling the integrity of intestinal homeostasis. It has been proposed that ROS, K⁺ efflux, and Ca²⁺ signaling activate NLRP3, however the precise mechanism is still unknown.

The NLRP3 driven inflammasome gets activated by cytosolic ROS generated by NADPH, but the exact involvement of ROS in this process is still up for debate. However, multiple experimental investigations have pointed that this inflammasome gets normally activated in macrophages deficient in NADPH oxidase. Consequently, the role of ROS in this inflammasome is unknown and that further investigation into this process is required. Moreover, there is currently no solution available for the first time when Psoriatic arthritis appears or a way to stop systemic and extracutaneous symptoms from developing. The evidence gathered through several studies highlights the significance of AIM2 and NLRP3 in the pathophysiology of psoriasis and its systemic symptoms, as well as the substantial upregulation of inflammasome genes in psoriatic epidermis. The NLRP3 inflammasome, which is made up of the pyrin domain-containing protein 3, leucine-rich repeat, and nucleotide-binding oligomerization domain, has become a key therapeutic target for a number of inflammatory illnesses and a crucial mediator of pathological inflammation. Psoriasis, a persistent inflammatory skin disorder that has no known therapy, has demonstrated encouraging outcomes in animal models by inhibiting the NLRP3 inflammasome. Skin problems are becoming more common as a result of environmental issues, growing mental stress, and population aging. At the same time, people's demand for effective skin disease treatments is growing due to the quick economic growth and rise in living conditions. Skin problems are becoming more common as a result of environmental issues, growing mental stress, and population aging. At the same time, people's demand for effective skin disease treatments is growing due to the quick economic growth and rise in living conditions. However, although the precise function of inflammasomes and how their components is initiating the psoriasis cascade is yet unknown, identifying early immune system triggers may yield new and potential therapeutic options for psoriasis prevention and better management.

Author Contributions

SP: Data curation, writing original draft, Reviewing and Editing & Figure preparation. Aryan & AH : Data curation, Reviewing and Editing; VC & SK: Conceptualisation, Reviewing and Editing, SP: Visualization, and Supervision.

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Ethical Approval

Not applicable.

Conflict of Interest

The authors declare no competing interests.

REFERENCES

1. Campanati A, Marani A, Martina E, Diotallevi F, Radi G, Offidani A. Psoriasis as an immune-mediated and inflammatory systemic disease: from pathophysiology to novel therapeutic approaches. *Biomedicines*. 2021;9(11):1511. doi:10.3390/biomedicines9111511
2. Unissa R, Kumar PM, Pasha M, Begum S, Maheswari B. Psoriasis: a comprehensive review. *Asian J Res Pharm Sci*. 2019;9(1):29-38. doi:10.5958/2231-5659.2019.00005.5
3. Raharja A, Mahil SK, Barker JN. Psoriasis: a brief overview. *Clin Med (Lond)*. 2021;21(3):170-173. doi:10.7861/clinmed.2021-0257
4. Deng Y, Chang C, Lu Q. The inflammatory response in psoriasis: a comprehensive review. *Clin Rev Allergy Immunol*. 2016;50(3):377-389. doi:10.1007/s12016-016-8535-x
5. Liu T, Li S, Ying S, et al. The IL-23/IL-17 pathway in inflammatory skin diseases: from bench to bedside. *Front Immunol*. 2020;11:594735. doi:10.3389/fimmu.2020.594735
6. Chiricozzi A, Krueger JG, Guttman-Yassky E. Pathogenic T cells in psoriasis and inflammatory skin diseases. *J Allergy Clin Immunol*. 2020;146(1):234-236. doi:10.1016/j.jaci.2020.04.001
7. Ozaki E, Campbell M, Doyle SL. Targeting the NLRP3 inflammasome in chronic inflammatory diseases: current perspectives. *J Inflamm Res*. 2015;8:15-27. doi:10.2147/JIR.S51250
8. Seok JK, Kang HC, Cho YY, Lee HS, Lee JY. Therapeutic regulation of the NLRP3 inflammasome in chronic inflammatory diseases. *Arch Pharm Res*. 2021;44(1):16-35. doi:10.1007/s12272-021-01307-9
9. Chen X, Deng G, Chen K, Chen Y, Ye W, Sun P. Targeting the NLRP3 inflammasome in

- psoriasis. *Int J Dermatol.* 2024;63(7):844-851. doi:10.1111/ijd.17073
10. Swanson KV, Deng M, Ting JP. The NLRP3 inflammasome: molecular activation and regulation to therapeutics. *Nat Rev Immunol.* 2019;19(8):477-489. doi:10.1038/s41577-019-0165-0
11. Smith CH, Yiu ZZN, Bale T, et al. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2023: a pragmatic update. *Br J Dermatol.* 2024;190(2):270-272. doi:10.1093/bjd/ljad347
12. Zhang Y, Liu L, Sun X, et al. Updated evidence of the association between elevated serum uric acid level and psoriasis. *Front Med (Lausanne).* 2021;8:645550. doi:10.3389/fmed.2021.645550
13. Suceveanu AI, Mazilu L, Katsiki N, et al. NLRP3 inflammasome biomarker-could be the new tool for improved cardiometabolic syndrome outcome. *Metabolites.* 2020;10(11):448. doi:10.3390/metabo10110448
14. Sutterwala FS, Haasken S, Cassel SL. Mechanism of NLRP3 inflammasome activation. *Ann N Y Acad Sci.* 2014;1319(1):82-95. doi:10.1111/nyas.12458
15. Zhang Y, Dong Z, Song W. NLRP3 inflammasome as a novel therapeutic target for Alzheimer's disease. *Signal Transduct Target Ther.* 2020;5(1):37. doi:10.1038/s41392-020-0145-7
16. Ciężżyńska M, Olejniczak-Staruch I, Sobolewska-Sztychny D, Narbutt J, Skibińska M, Lesiak A. The Role of NLRP1, NLRP3, and AIM2 Inflammasomes in Psoriasis: Review. *International Journal of Molecular Sciences.* 2021; 22(11):5898. <https://doi.org/10.3390/ijms22115898>
17. Rajamäki K, Nordström T, Nurmi K, et al. Extracellular acidosis is a novel danger signal alerting innate immunity via the NLRP3 inflammasome. *J Biol Chem.* 2013;288(19):13410-13419. doi:10.1074/jbc.M112.426254
18. Fu J, Wu H. Structural mechanisms of NLRP3 inflammasome assembly and activation. *Annu Rev Immunol.* 2023;41:301-316. doi:10.1146/annurev-immunol-081022-021207
19. Lu A, Wu H. Structural mechanisms of inflammasome assembly. *FEBS J.* 2015;282(3):435-444. doi:10.1111/febs.13133
20. Ferrari D, Casciano F, Secchiero P, Reali E. Purinergic signaling and inflammasome activation in psoriasis pathogenesis. *Int J Mol Sci.* 2021;22(17):9449. doi:10.3390/ijms22179449
21. Paik S, Kim JK, Silwal P, Sasakawa C, Jo EK. An update on the regulatory mechanisms of NLRP3 inflammasome activation. *Cell Mol Immunol.* 2021;18(5):1141-1160. doi:10.1038/s41423-021-00670-3
22. Li Y, Jiang Q. Uncoupled pyroptosis and IL-1 β secretion downstream of inflammasome signaling. *Front Immunol.* 2023;14:1128358. doi:10.3389/fimmu.2023.1128358
23. Terranova C, Spitilli A, Camporeale A, et al. Skin Application of Inflammasome Inhibitor MCC950 Prevents Psoriasis-like Cutaneous Manifestations and Associated Systemic Inflammation. *Inflammation.* 2026;49(1):173. Published 2026 Jun 4. doi:10.1007/s10753-026-02535-1
24. Zhang C, Tang B, Zheng X, et al. Analysis of the potential pyroptosis mechanism in psoriasis and experimental validation of NLRP3 in vitro and in vivo. *Int Immunopharmacol.* 2023;124(Pt A):110811. doi:10.1016/j.intimp.2023.110811
25. Li H, Liu T, Shi X, et al. Mechanisms and therapeutic potential of pharmacological agents targeting inflammasomes. *Biomed Pharmacother.* 2025;189:118164. doi:10.1016/j.biopha.2025.118164
26. Wang Y, Liu YJ, Zhang MM, et al. CY-09 Alleviates the Depression-like Behaviors via Inhibiting NLRP3 Inflammasome-Mediated Neuroinflammation in Lipopolysaccharide-Induced Mice. *ACS Chem Neurosci.* 2022;13(23):3291-3302. doi:10.1021/acscchemneuro.2c00348
27. Zhang Y, Lin Z, Chen D, He Y. CY-09 attenuates the progression of osteoarthritis via inhibiting NLRP3 inflammasome-mediated pyroptosis. *Biochem Biophys Res Commun.* 2021;553:119-125. doi:10.1016/j.bbrc.2021.03.055
28. Fan Y, Xue G, Chen Q, Lu Y, Dong R, Yuan H. CY-09 Inhibits NLRP3 Inflammasome Activation to Relieve Pain via TRPA1 [retracted in: Comput Math Methods Med. 2023 Aug 2;2023:9759851. doi:

- 10.1155/2023/9759851.]. *Comput Math Methods Med.* 2021;2021:9806690. Published 2021 Aug 14. doi:10.1155/2021/9806690
29. Shi A, Shu Y, Hu K, Sudesh S, Tu Y. NLRP3-inflammasome related genes as emerging biomarkers and therapeutic targets in psoriasis. *Inflammation.* 2025;48(5):3366-3378. doi:10.1007/s10753-025-02271-y
30. Zahid, A., Li, B., Kombe, A. J. K., Jin, T., & Tao, J. (2019). Pharmacological Inhibitors of the NLRP3 Inflammasome. *Frontiers in immunology*, 10, 2538. <https://doi.org/10.3389/fimmu.2019.02538>
31. Zou C, Jiang S, Li H, Zhao K, Cao D, Yang G. The NLRP3 Inflammasome: Mechanisms of Activation, Regulation, and Therapeutic Opportunities. *MedComm* (2020). 2026;7(3):e70660. Published 2026 Mar 5. doi:10.1002/mco2.70660
32. Alalwan TA, Aksal R, Allehdan S, Rondanelli M, Perna S. Effect of (poly)phenols as potential agents in the treatment of psoriasis: A systematic review of the evidence and future applications. *Nutraceuticals.* 2025;5(3):24. doi:10.3390/nutraceuticals5030024
33. Zhang J, Ma Y, Li W. Curcumin reduces inflammation in mice with the psoriasis model by inhibiting NLRP3 inflammatory bodies. *Cell Mol Biol (Noisy-le-grand).* 2022;67(6):48-54. Published 2022 Feb 27. doi:10.14715/cmb/2021.67.6.7
34. Paolino G, Di Nicola MR, Currado M, Brianti P, Mercuri SR. Serum tryptase levels in patients with psoriasis: a pilot study for a possible useful biomarker. *Clin Exp Dermatol.* 2022;47(1):178-179. doi:10.1111/ced.14874
35. Cui Q, Wang H. Resveratrol in Dermatological Therapy: A Critical Review of Mechanisms, Delivery Innovations, and Clinical Frontiers. *Clin Cosmet Investig Dermatol.* 2025;18:2229-2242. Published 2025 Sep 9. doi:10.2147/CCID.S543849
36. Shi A, Shu Y, Hu K, Sudesh S, Tu Y. NLRP3-inflammasome Related Genes as Emerging Biomarkers and Therapeutic Targets in Psoriasis. *Inflammation.* 2025;48(5):3366-3378. doi:10.1007/s10753-025-02271
37. Sul OJ, Ra SW. Quercetin Prevents LPS-Induced Oxidative Stress and Inflammation by Modulating NOX2/ROS/NF- κ B in Lung Epithelial Cells. *Molecules.* 2021;26(22):6949. Published 2021 Nov 17. doi:10.3390/molecules26226949
38. Wu J, Lv T, Liu Y, et al. The role of quercetin in NLRP3-associated inflammation. *Inflammopharmacology.* 2024;32(6):3585-3610. doi:10.1007/s10787-024-01566-0
39. Beken B, Serttas R, Yazicioglu M, Turkekul K, Erdogan S. Quercetin Improves Inflammation, Oxidative Stress, and Impaired Wound Healing in Atopic Dermatitis Model of Human Keratinocytes. *Pediatr Allergy Immunol Pulmonol.* 2020;33(2):69-79. doi:10.1089/ped.2019.
40. Nisar A, Jagtap S, Vyavahare S, et al. Phytochemicals in the treatment of inflammation-associated diseases: the journey from preclinical trials to clinical practice. *Front Pharmacol.* 2023;14:1177050. Published 2023 May 9. doi:10.3389/fphar.2023.1177050
41. Feng Y, Zhang X, Li J, et al. Ultra-small quercetin-based nanotherapeutics ameliorate acute liver failure by combatting inflammation/cellular senescence cycle. *Theranostics.* 2025;15(3):1035-1056. Published 2025 Jan 1. doi:10.7150/thno.103746
42. Chen H, Lu C, Liu H, et al. Quercetin ameliorates imiquimod-induced psoriasis-like skin inflammation in mice via the NF- κ B pathway. *Int Immunopharmacol.* 2017;48:110-117. doi:10.1016/j.intimp.2017.04.022
43. Toldo S, Abbate A. The role of the NLRP3 inflammasome and pyroptosis in cardiovascular diseases. *Nat Rev Cardiol.* 2024;21(4):219-237. doi:10.1038/s41569-023-00946-3
44. Coll RC, Schroder K, Pelegrín P. NLRP3 and pyroptosis blockers for treating inflammatory diseases. *Trends Pharmacol Sci.* 2022;43(8):653-668. doi:10.1016/j.tips.2022.04.003
45. Hasan AA, Tatarskiy V, Kalinina E. Synthetic pathways and the therapeutic potential of quercetin and curcumin. *Int J Mol Sci.* 2022;23(22):14413. doi:10.3390/ijms232214413
46. Wang D, Duncan B, Li X, Shi J. The role of NLRP3 inflammasome in infection-related, immune-mediated and autoimmune skin

- diseases. *J Dermatol Sci.* 2020;98(3):146-151. doi:10.1016/j.jdermsci.2020.03.001
47. Cui Q, Wang H. Resveratrol in dermatological therapy: a critical review of mechanisms, delivery innovations, and clinical frontiers. *Clin Cosmet Investig Dermatol.* 2025;18:2229-2242. doi:10.2147/CCID.S543849
48. Nisar A, Jagtap S, Vyavahare S, et al. Phytochemicals in the treatment of inflammation-associated diseases: the journey from preclinical trials to clinical practice. *Front Pharmacol.* 2023;14:1177050. doi:10.3389/fphar.2023.1177050
49. Wu J, Lv T, Liu Y, et al. The role of quercetin in NLRP3-associated inflammation. *Inflammopharmacology.* 2024;32(6):3585-3610. doi:10.1007/s10787-024-01566-0
50. Shao BZ, Xu ZQ, Han BZ, Su DF, Liu C. NLRP3 inflammasome and its inhibitors: a review. *Front Pharmacol.* 2015;6:262. doi:10.3389/fphar.2015.00262
51. Bagherniya M, Khedmatgozar H, Fakheran O, Xu S, Johnston TP, Sahebkar A. Medicinal plants and bioactive natural products as inhibitors of NLRP3 inflammasome. *Phytother Res.* 2021;35(9):4804-4833. doi:10.1002/ptr.7118
52. Di Filippo M, Karakaya T, Slafova M, et al. NLRP1 inflammasome activation in skin equivalents reveals mechanistic insights into the roles of keratinocytes in psoriasis. *Cell Death Dis.* 2026;17(1):670. doi:10.1038/s41419-026-08908-6
53. Bu J, Ding R, Zhou L, Chen X, Shen E. Epidemiology of psoriasis and comorbid diseases: a narrative review. *Front Immunol.* 2022;13:880201. doi:10.3389/fimmu.2022.880201
54. Verma D, Fekri SZ, Sigurdardottir G, Bivik Eding C, Sandin C, Enerbäck C. Enhanced inflammasome activity in patients with psoriasis promotes systemic inflammation. *J Invest Dermatol.* 2021;141(3):586-595.e5. doi:10.1016/j.jid.2020.07.012
55. Shahi A, Afzali S, Amirzargar A, Mohaghegh P, Salehi S, Mansoori Y. Potential roles of inflammasomes in the pathophysiology of psoriasis: a comprehensive review. *Mol Immunol.* 2023;161:44-60. doi:10.1016/j.molimm.2023.06.007
56. Ramessur R, Corbett M, Marshall D, et al. Biomarkers of disease progression in people with psoriasis: a scoping review. *Br J Dermatol.* 2022;187(4):481-493. doi:10.1111/bjd.21627
57. Yadalam PK, Natarajan PM, Ardila CM. Variational graph autoencoder for reconstructed transcriptomic data associated with NLRP3 mediated pyroptosis in periodontitis. *Sci Rep.* 2025;15(1):1962. doi:10.1038/s41598-025-86455-4
58. Baldwin AG, Brough D, Freeman S. Inhibiting the Inflammasome: A Chemical Perspective. *J Med Chem.* 2016;59(5):1691-1710. doi:10.1021/acs.jmedchem.5b01091