Received: 12 August 2024 | Revised: 19 September 2024 | Accepted: 6 October 2024 | Published online: 11 October 2024

International Journal of Advance in Clinical Science Research, Volume 3, 2024
https://h-tsp.com/

Research Progress of Chinese Medicine Monomer and Compound in the Treatment of Psoriasis by Regulating NF-κB Signaling Pathway

Zhengjin Zhu[1], Liqian He[1], Xudong Wang[1], Chanjuan Yan[2], Wenbin Li[2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Shaanxi Provincial Hospital of Chinese Medicine, Xi'an 710003, Shaanxi, China
Author to whom correspondence should be addressed.

Abstract: ***Psoriasis is an immune-mediated inflammatory skin disease influenced by both genetic and environmental factors, marked by its chronicity, recurrence, and treatment resistance. Its pathogenesis is highly complex, encompassing a variety of genes, cytokines, and signaling pathways. Advances in the study of biological signaling pathways have revealed the NF-κB signaling pathway's involvement in the inflammatory response, cell proliferation, and apoptosis in psoriasis, positioning it as a potential therapeutic target. In recent years, the modern research and innovation of traditional Chinese medicine have advanced, showcasing significant therapeutic efficacy due to its multi-pathway, multi-target, and multi-component nature. A review of international literature reveals that traditional Chinese medicine monomers, active ingredients, and formulations can modulate the NF-κB signaling pathway, thereby reducing inflammatory responses, suppressing cell proliferation, modulating immunity, and managing oxidative stress to treat psoriasis. This article thus summarizes recent advancements in the use of traditional Chinese medicine monomers and compounds to modulate the NF-κB signaling pathway in the treatment of psoriasis, offering insights into the potential mechanisms of traditional Chinese medicine in this field.***

Keywords: Chinese medicine monomer; Compound Chinese medicine; Psoriasis; NF-κB signaling pathway; Mechanism.

1. Introduction

Psoriasis is an immunologically mediated inflammatory skin disease that results from the interaction of genetic and environmental factors. Clinically, it is characterized by the appearance of scaly erythematous plaques or patches at the sites of skin damage. This condition is chronic, prone to relapses, and difficult to cure completely [1,2]. According to surveys, the global prevalence of psoriasis is as high as 3% [3], affecting over 125 million people worldwide [4]. In 2017, the incidence rate of psoriasis in China was 69.2 per 100,000 people, and it has been showing a continuous upward trend year by year [5]. Due to its frequent comorbidity with psychological disorders, metabolic diseases, cardiovascular diseases, etc. [6], it severely affects the physical and mental health as well as the quality of life of patients. The pathogenesis of psoriasis is not yet fully understood, but current research

suggests that it is related to factors such as inflammatory cell infiltration, hyperplasia of keratinocytes (KC), parakeratosis, and immune dysregulation [7,8]. The pathogenesis of psoriasis involves multiple signaling pathways, including the mitogen-activated protein kinase (MAPK) signaling pathway, nuclear factor-kappa B (NF-κB) signaling pathway, Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway, etc. Among them, the classical inflammatory signaling pathway NF-κB can participate in the inflammatory response, cell proliferation, and apoptosis of psoriasis, and is a key pathway leading to the occurrence and development of psoriasis [9].

The treatment of psoriasis remains a challenging issue in the medical community. Although the widespread use of biologics has significantly improved clinical efficacy [10], their adverse reactions and high cost have reduced patient acceptance. In recent years, traditional Chinese medicine has increasingly demonstrated unique advantages in the treatment of psoriasis. As more researchers delve into the study of Chinese herbal medicine, they have found that single Chinese medicinal herbs, active components, and compound formulas possess characteristics such as multi-pathway, multi-target, and multi-component [11,12], playing a key role in the treatment of psoriasis. Therefore, this article reviews the research on the regulation of the NF-κB signaling pathway by Chinese medicinal monomers and compound formulas in the treatment of psoriasis in recent years, both domestically and internationally.

2. Overview of the NF-κB Signaling Pathway

NF-κB is an important intracellular dimeric transcription factor that participates in a variety of biological processes, including inflammatory responses, immune responses, cell proliferation and apoptosis, tumor formation, and memory-related activities [13, 14]. The NF-κB family consists of five members: RelA (p65), RelB, c-Rel, NF-κB2 (p100/p52), and NF-κB1 (p105/p50) [15]. Due to the presence of a common Rel homology domain (RHD) at the N-terminus of all members, any member of the NF-κB family can form homodimers or heterodimers, with the most common being the heterodimer formed by RelA (p65) and NF-κB1 (p50) [16]. RelA, RelB, and c-Rel contain transcriptional activation domains (TADs) that can activate target genes, while the p52 and p50 homodimers lack TADs and exist as transcriptional repressors [17]. The NF-κB signaling pathway is composed of receptors and proximal signaling adaptors, NF-κB inhibitory proteins (IkB proteins), IkB kinase (IKK) complexes, and NF-κB dimers [18]. This pathway can be activated by various stimuli, such as cytokines, immune cells, bacterial and viral products, ultraviolet light, and ionizing radiation [16]. Key factors in the transmission and regulation of the classical NF-κB signaling pathway include tumor necrosis factor-α (TNF-α) [19, 20], interleukin-1β (IL-1β) [21], lipopolysaccharide (LPS) [22], and antigens [23], which bind to cell surface receptors and activate the NF-κB pathway through the action of multiple bridging proteins [24]. In a resting state, IkB proteins inhibit the activity of p65 and p50, maintaining them in a stable state in the cytoplasm as a trimeric complex p50-p65-IkB [25]. Upon cellular stimulation by various intracellular and extracellular stimuli, the IKK is activated, leading to the phosphorylation of the conserved serine residues of IkB, ubiquitination by the SCF E3 ubiquitin ligase, and subsequent degradation of IkB. The NF-κB dimer is then released, translocates to the nucleus, binds to its associated DNA motifs, and activates the transcription of downstream target genes, thus forming the classical NF-κB signaling pathway [24,26].

3. The Mechanism of NF-κB Signaling Pathway in Psoriasis

The pathogenesis of psoriasis is complex, involving the interplay between T cells, dendritic cells (DCs), keratinocytes (KCs), macrophages, and inflammatory cytokines. Studies have found that there is a large number of CD4+ T cells in the skin lesions of psoriasis patients [27]. CD4+ T cells can be divided into Th1, Th2, Th17, etc., among which Th1 can enhance the immune response mediated by

macrophages and cytotoxic T cells by releasing interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), playing a crucial role in the development of psoriasis [28]. In the early stages of psoriasis, damaged KCs release self-nucleotides and antimicrobial peptides to activate plasmacytoid dendritic cells (pDCs) and macrophages, which then produce inflammatory factors such as IFN-γ, IFN-α, TNF-α, and IL-1β. Under the synergistic action of various inflammatory factors, KC proliferation and abnormal differentiation can be induced, leading to the production of chemokines that recruit Th17 cells, DCs, macrophages, and other immune cells to damage the skin, maintaining the continuous development of psoriasis inflammation [29,30]. Samples from the skin lesions and non-lesional areas of psoriasis patients show that, compared with non-lesional samples, the phosphorylation level and activity of NF-κB in the lesional area are significantly increased [31]. Studies have shown that the NF-κB signaling pathway is involved in the pathogenesis of psoriasis in various cell types. In CD4+ T cells, the NF-κB signaling pathway, including RelA and c-Rel, can induce the differentiation of Th17 cells by inducing the expression of RORγ T, thereby mediating the occurrence of psoriasis [32]. In DCs, the NF-κB signaling pathway plays an important role in the production of IL-23 in psoriasis models[33]. In KCs, the activated NF-κB signaling pathway can induce acanthosis and hyperkeratosis in psoriasis lesions, which is consistent with the key role of the typical NF-κB signal in signal transduction mediated by TNF-α receptors and IL-17 receptors [34,35]. Kazumasa Suzuki et al. [36] used imiquimod to induce a psoriasis model in NF-κB1-deficient mice and their littermate wild-type (WT) mice, and found that the number of Vγ4(+)Vδ4(+)γδT17 cells in the skin tissue of NF-κB1-deficient mice was significantly reduced compared to WT mice. It was also found that NF-κB1 can play an important role in the pathogenesis of imiquimod-induced psoriasis-like skin inflammation by promoting the proliferation of Vγ4(+)Vδ4(+)γδT17 cells. In summary, the NF-κB signaling pathway is closely related to the occurrence and development of psoriasis and is a key target for its treatment.

4. Regulation of the NF-κB Signaling Pathway by Chinese Medicinal Monomers and Compounds for the Improvement of Psoriasis

Psoriasis belongs to the category of "Bai Bi" in traditional Chinese medicine. According to the "Treatise on the Origins and Symptoms of Diseases": "Dry ringworm, but with a border, the skin is withered and thin, itchy, and white flakes come out when scratched. This is all due to the wind, cold, and damp evils, which reside in the interstitial spaces and are combined with cold and dampness, and are born in conjunction with the blood and qi." It points out that the disease is caused by the wind, cold, and damp evils fighting with the blood and qi. With the continuous summarization and accumulation of experience in treating psoriasis by doctors of all dynasties, it is widely recognized that the pathogenesis of the disease is based on three types of blood heat, blood stasis, and blood dryness, among which blood heat syndrome is the most common and is the core pathological link in the early stage of psoriasis [37]. By summarizing the literature on the intervention of the NF-κB signaling pathway in the treatment of psoriasis by Chinese medicinal monomers and compounds, it has been found that the Chinese medicinal monomers are mostly heat-clearing and detoxifying herbs such as licorice, honeysuckle, chrysanthemum, scutellaria, rehmannia, dragon's head, lithospermum, and red peony, followed by Chinese medicines with the effect of promoting blood circulation and removing blood stasis such as red peony, chuanxiong, notoginseng, and curcumin, with flavonoid compounds as the main effective components. Chinese compound prescriptions are mostly based on the treatment of heat-clearing and detoxifying, while also nourishing blood and promoting blood circulation, which is also in line with the etiology and pathogenesis of psoriasis.

4.1 Chinese Medicinal Monomers and Active Components

Chuanxiongzine is an alkaloid compound extracted from the Chinese medicine Chuanxiong, which

has anti-inflammatory, antibacterial, and anti-cancer effects [38]. Jiang et al. [39] found through in vivo and in vitro experiments that Chuanxiongzine can reduce the expression levels of inflammatory factors TNF-α, IL-6, IL-17A, IL-22, and IL-23 in the imiquimod-induced psoriasis mouse model, significantly downregulate the expression of phosphorylated nuclear transcription factor-κB inhibitor (p-IκB), phosphorylated nuclear transcription factor-κB p65 (p-NF-κB p65), TNF receptor-associated factor 6 (TRAF6), and oncogene jun (c-jun) proteins induced by IL-17A in HaCaT cells, while reducing the expression of keratinocyte S100A7 and S100A8, intervening in the activation of the TRAF6/c-JUN/NF-κB signaling pathway, inhibiting the proliferation of KCs, and alleviating the inflammatory response of psoriasis.

Shaoyaogan is extracted from the Chinese medicine red peony and white peony, belonging to the monoterpene compounds, with good anti-inflammatory, immune regulation, and antioxidant effects [40]. Bai et al. [41] found that Shaoyaogan can downregulate the mRNA levels of pro-inflammatory factors TNF-α, IL-17, IL-22, IL-23, and the expression of keratin 17 (K17) in the imiquimod-induced psoriasis mouse model, inhibit the expression of p-NF-κB p65 and p-IkB induced by inflammatory factors in HaCaT cells, indicating that Shaoyaogan can inhibit the NF-κB signaling pathway, thereby inhibiting the proliferation of KCs, reducing the expression levels of inflammatory factors, and improving the symptoms of psoriasis.

Galangin is a flavonoid compound extracted from the root of the Chinese medicine Kaempferia galanga, with good anti-inflammatory, antibacterial, antioxidant, and anti-aging effects [42]. Rajendra-Sangaraju et al. [43] showed that Galangin can significantly reduce the levels of pro-inflammatory factors IL-17, IL-1β, IL-23, IL-6, TNF-α in the serum and skin lesions of the imiquimod-induced psoriasis mouse model, increase the level of anti-inflammatory factor IL-10, downregulate the expression of p-IkBα protein in the skin lesions, and upregulate the level of heme oxygenase-1 (HO-1), inhibiting the NF-κB and activating the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathways, achieving anti-inflammatory and antioxidant effects, thereby improving the skin lesions of psoriasis.

Licorice has been discovered through modern pharmacological research to possess anti-inflammatory, antibacterial, antiviral, antitumor, and immune-modulating effects. Glycyrrhizic acid and isoliquiritin, both flavonoid compounds extracted from licorice, are widely used in the clinical treatment of various diseases [44]. Guo et al. [45] found in their study on the effects of glycyrrhizic acid in an imiquimod-induced psoriasis mouse model that it could inhibit the phosphorylation of NF-κB p65 and c-Fos, as well as the polarization of Th17 cells. It reduced the production of IL-17A, IL-23, IL-6, and TNF-α in the skin lesions of the psoriasis model mice, hindering the activation of the NF-κB and activator protein 1 (AP-1) pathways, thereby playing a role in the treatment of psoriasis. Wu et al. [46] demonstrated that isoliquiritin could decrease the expression of NF-κB protein and mRNA in a psoriasis mouse model, downregulate the levels of inflammatory factors IL-6 and IL-8, suggesting that isoliquiritin could improve the inflammatory response of psoriasis skin lesions by suppressing the activity of the NF-κB signaling pathway.

Ginsenoside Rg1, an active ingredient extracted from the traditional Chinese medicine ginseng, is a tetracyclic triterpene saponin known for its anti-inflammatory, anti-apoptotic, antioxidant, immune-modulating, and neuroprotective effects [47]. Shi et al. [48] discovered that ginsenoside Rg1 could reduce the levels of IL-23, IL-22, IL-17A, IL-1β, and TNF-α in the skin lesions of an imiquimod-induced psoriasis mouse model, as well as the expression of P-IκB and NF-κB p65 proteins. It exerts a therapeutic effect on psoriasis by downregulating the NF-κB signaling pathway and inhibiting the inflammatory response.

Curcumin, derived from the active components of the traditional Chinese medicine turmeric, is a sesquiterpene compound with anti-inflammatory, immune-modulating, and antitumor effects [49]. Li et al. [50] showed that curcumin could improve the symptoms of skin lesions in an imiquimod-induced psoriasis mouse model and reduce the PASI score. The mechanism involves the inhibition of the NF-κB and MAPK signaling pathways, leading to a decrease in the expression of CD8+ T cells and cyclooxygenase-2 (COX-2), and the suppression of pro-inflammatory factors IL-17, IL-22, and IL-23. This suggests that curcumin could improve psoriasis symptoms by downregulating downstream inflammatory factors and modulating immune cells through the inhibition of NF-κB and MAPK signaling pathways.

Kaempferol, a natural flavonoid compound extracted from Kaempferia galanga, possesses anti-inflammatory, antibacterial, antioxidant, and antitumor properties [51]. Liu et al. [52] found that kaempferol significantly improved the morphological and histopathological changes of skin lesions in an imiquimod-induced psoriasis mouse model. It reduced the mRNA expression levels of IL-17A, IL-6, and TNF-α in the tissue, upregulated the mRNA expression of IL-10 and forkhead box P3 (FoxP3), and decreased the frequency of IL-17A+ CD4+ and RORγt+ CD4+ cells as well as the expression of NF-κB p65. The mechanism is that kaempferol obstructs the activation of the NF-κB pathway, inhibits the formation of Th17 cells, reduces pro-inflammatory factors, and increases anti-inflammatory factor levels, thereby improving skin lesions.

Daphnetin, an effective component extracted from the traditional Chinese medicine Daphne odora, belongs to the class of benzopyranone compounds and has been found to have anti-inflammatory, antioxidant, antibacterial, and neuroprotective effects [53]. Gao et al. [54] used daphnetin to intervene in an in vitro psoriasis model established by M5-induced HaCaT keratinocytes and found that it could downregulate the expression of keratin 6 (KRT6), monocyte chemoattractant protein-1 (MCP-1), and cytokines IL-1β, IL-6, IL-8, TNF-α, and IL-23A, and inhibit the phosphorylation and nuclear translocation of NF-κB p65. This suggests that daphnetin can impede the activity of the NF-κB signaling pathway, thereby inhibiting excessive keratinocyte proliferation, reducing the expression levels of inflammatory cytokines, and achieving the effect of treating psoriasis.

Luteolin is a natural flavonoid compound extracted from various traditional Chinese medicinal herbs such as honeysuckle, schizonepeta, and chrysanthemum. It possesses anti-inflammatory, antiallergic, antioxidant, and antitumor effects [55]. Zhou et al. [56] conducted both animal and cellular experiments and concluded that luteolin ameliorates the pathological changes in imiquimod-induced psoriasis mouse models, significantly reducing the numbers of tissue macrophages (F4/80+), T cells (CD8+), and neutrophils (GR1+). It also decreases the levels of serum and tissue TNF-α, IL-23, IL-17A, IL-6, and IL-1. In vitro, it downregulates the expression of COX-2, inducible nitric oxide synthase (iNOS), and NF-κB p65 induced by LPS in macrophages Raw264.7. This suggests that luteolin may alleviate the inflammatory response in psoriasis by blocking the expression and activation of NF-κB, reducing macrophage infiltration, and inhibiting the release of downstream inflammatory mediators.

Baicalin, a flavonoid compound extracted from the traditional Chinese medicine Scutellaria baicalensis, has anti-inflammatory, antiallergic, antiviral, and antitumor properties [57]. Wu et al. [58] found that baicalin can inhibit the STAT3/NF-κB signaling pathway in an in vitro psoriasis model established with TNF-α-induced HaCaT cells. It downregulates the expression of inflammatory cytokines TNF-α, IFN-γ, IL-22, IL-1β, IL-4, and IL-6 and inhibits keratinocyte proliferation, thereby reducing the symptoms of psoriasis lesions.

Additionally, Liu et al. [59] discovered that the active component of Rehmannia glutinosa, catalpol, can improve oxidative stress and inflammatory responses in psoriasis by inhibiting SIRT1-mediated NF-κB and MAPKs signaling pathways. Chen et al. [60] found that quercetin, a flavonoid compound extracted from traditional Chinese medicines such as Panax notoginseng, mulberry leaf, and Bupleurum, can effectively reduce the levels of pro-inflammatory factors IL-6, TNF-α, and IL-17 in imiquimod-induced psoriasis mouse models, with its mechanism related to the suppression of the NF-κB signaling pathway. Yang et al. [61] demonstrated that solasodine, an effective component of Solanum nigrum and Fritillaria, can reduce T cell and macrophage infiltration in the skin lesions of imiquimod-induced psoriasis mouse models, decrease the level of TNF-α, inhibit the activation of NF-κB p65, and the expression of IL-17A and IL-33. The mechanism is the obstruction of NF-κB signaling pathway activation. Chen et al. [62] used pomegranate peel extract, punicalagin, to intervene in a psoriasis mouse model and found that it can reduce the levels of pro-inflammatory factors TNF-α, IL-6, IL-1β, IL-8, IL-17, and IL-23 in serum and skin lesions, as well as the expression of CD3 and Ki67 in the lesions. The results indicate that the mechanism is achieved through the inhibition of NF-κB and STAT3 signaling pathways. Zhou Mingming [63] showed that shikonin, extracted from traditional Chinese medicine Lithospermum erythrorhizon, can downregulate the mRNA of TNF-α, IL-6, IL-1β, and the expression of NF-κB p65 protein in imiquimod-induced psoriasis mouse models, suggesting that shikonin can alleviate the inflammatory response of psoriasis by inhibiting the NF-κB signaling pathway and intervening in the levels of pro-inflammatory factors. Wang Mei et al. [64] found that naringin, a flavonoid compound extracted from traditional Chinese medicines such as Citrus reticulata, Aurantium fruit, and Citrus aurantium, can reduce the transcription levels of pro-inflammatory factors TNF-α, IL-6, IL-1β, and IL-17 in LPS-induced HaCaT cells, significantly inhibit the expression of phosphorylated proteins P38 MAPK and NF-κB p65, and improve clinical symptoms of psoriasis by regulating the MAPK/NF-κB signaling pathway.The mechanisms by which Chinese medicinal monomers and active components regulate the NF-κB signaling pathway to treat psoriasis are shown in Table 1.

Table 1: Mechanisms of Chinese medicine monomers and active ingredients in the treatment of psoriasis by regulating the NF-κB signaling pathway

Chinese medicine	active ingredients	Mechanism	Study
Chuanxiong	Chuanxiongzine	[TNF-α、IL-6、IL-17A、IL-22、IL-23]↑，[S100A7、S100A8，p-IkB、p-NF-κB p65、TRAF6、c-jun]↓	[39]
Shaoyao	Shaoyaogan	[TNF-α、IL-17、IL-22、IL-23、K17]↑，[p-NF-κB p65、p-IkB]↓	[41]
galangal	Galangin	[IL-17、IL-1β、IL-23、IL-6、TNF-α]↓，[IL-10、HO-1]↑，p-IkBα↓，Nrf2↑	[43]
Licorice	Glycyrrhizic	[IL-17A、IL-23、IL-6、TNF-α]↓，[NF-κB p65、c-Fos，AP-1，Th17]↓	[45]
	isoliquiritin	[IL-6、IL-8]↓，NF-κB↓	[46]
Ginseng root	Ginsenoside Rg1	[IL-23、IL-22、IL-17A、IL-1β、TNF-α]↓，[P-IκB、NF-κB p65]↓	[48]
Turmeric	Curcumin	[IL-17、IL-22、IL-23]↓，[$CD8^+$T、COX-2]↓，[MAPK、NF-κB]↓	[50]
Kaempferia	Kaempferol	[IL-17A、IL-6、TNF-α]↓，[IL-10、FoxP3 mRNA]↑，[IL-17A+ CD4+ 、RORγt+ CD4+]↓，[NF-κB p65、Th17]↓	[52]
daphne	Daphnetin	[IL-1β、IL-6、IL-8、TNF-α、IL-23A、MCP-1、KRT6]↓，NF-κB p65↓	[54]
Honeysuckle, schizonepod, chrysanthemum, etc	Luteolin	[TNF-α、IL-23、IL-17A、IL-6、IL-1]↓，[F4/80+、CD8+、GR1+]，[COX-2、iNOS、NF-κB p65]↓	[56]
Scutellaria baicalensis	Baicalin	[TNF-α、IFN-γ、IL-22、IL-1β、IL-4、IL-6]↓，STAT3/NF-κB↓	[58]
Rehmannia glutinosa	catalpol	[NF-κB、MAPKs]↓	[59]
Panax notoginseng,mulberry leaf,Bupleurum, etc	quercetin	[IL-6、TNF-α、IL-17]↓，NF-κB↓	[60]
Solanum nigrum,Fritillaria	solasodine	[TNF-α、IL-17A、IL-33]↓，NF-κB p65↓	[61]
pomegranate peel	punicalagin	[TNF-α、IL-6、IL-1β、IL-8、IL-17、IL-23、CD3、Ki67]↓，[NF-κB、STAT3]↓	[62]
Lithospermum erythrorhizon	shikonin	[TNF-α、IL-6、IL-1β m RNA]↓，NF-κB p65↓	[63]
Citrus reticulata, Aurantium fruit,Citrus aurantium, etc	naringin	[TNF-α、IL-6、IL-1β、IL-17]↓，[P38 MAPK、NF-κB p65]↓	[64]

4.2 Traditional Chinese Medicine Compounds

The formula "Nourishing Blood and Detoxifying Soup" is composed of Radix Angelicae Sinensis, Rehmannia glutinosa, Salvia miltiorrhiza, Spatholobus suberectus, Ophiopogon japonicus, Scrophularia ningpoensis, Trichosanthes kirilowii, Atractylodes macrocephala, Pueraria lobata, Oldenlandia diffusa, and others, and is known for its effects in nourishing blood, moistening dryness, eliminating dampness, and detoxifying [65]. Lv et al. [66] found that this soup significantly reduced the expression of proliferating cell nuclear antigen (PCNA), Ki67, and CD4+, CD8+ in the imiquimod-induced psoriasis mouse model. It also downregulated the levels of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β, IFN-γ, IL-17, and IL-23. The mechanism is suggested to be the inhibition of heat shock protein 70 (HSP70) secretion, blocking the activation of the TLR4/NF-κB signaling pathway, suppressing the release of downstream inflammatory mediators, modulating immune cells, and thereby inhibiting keratinocyte proliferation, which contributes to the alleviation of psoriasis symptoms.

The formula "Dan Shen Bai Bi Xiao" consists of Salvia miltiorrhiza, Buthus martensii, Zaocys dhumnades, Rheum palmatum, Cicada slough, Eupolyphaga sinensis, Cynanchum paniculatum, Crataegus pinnatifida, Isatis indigotica, Carthamus tinctorius, Saposhnikovia divaricata, Atractylodes macrocephala, and Glycyrrhiza uralensis, and is known for its effects in nourishing blood, promoting blood circulation, clearing heat, and detoxifying [67]. Jin et al. [68] demonstrated that "Dan Shen Bai Bi Xiao" intervention in the imiquimod-induced psoriasis mouse model significantly reduced the levels of inflammatory cytokines TNF-α, IL-17A, IL-23, IL-6, IL-1β, and IL-22 in mouse serum and downregulated the proteins NF-κB, STAT3, and MAPKs in the tissues. This suggests that "Dan Shen Bai Bi Xiao" can suppress the activation of the NF-κB, STAT3, and MAPKs signaling pathways, alleviate the release of pro-inflammatory factors, and mitigate the inflammatory response in psoriasis.

The "Xiao Yin Jie Du Granules" formula is made up of Rehmannia glutinosa, Moutan cortex, Paeonia lactiflora, Sophora japonica, Lithospermum erythrorhizon, Atractylodes macrocephala, Bos taurus domesticus gigas, Oldenlandia diffusa, Lonicerae japonicae, Isatis indigotica, and others, and is known for its effects in clearing heat and cooling blood, detoxifying, and dispersing stasis [69]. Wang et al. [70] found that "Xiao Yin Jie Du Granules" significantly reduced the expression of proliferation-related proteins K6, K16, K17, IL-36γ, and inflammatory factors IL-17, IL-22, and CD4+ T cells in the imiquimod-induced psoriasis mouse model. It also downregulated the expression of Sphingosine-1-phosphate receptor 1-5 (S1PR1-5), NF-κB p65, phosphorylated NF-κB p65 (p-NF-κB p65), IKKα, and phosphorylated IKKα (p-IKKα). The healing mechanism is associated with the inhibition of the S1P/S1PR-Th17/KC inflammatory reaction axis by "Xiao Yin Jie Du Granules" and the obstruction of the NF-κB signaling pathway activation.The mechanism of action of TCM compound in the treatment of psoriasis by regulating NF-κB signaling pathway is shown in Table 2.

Table 2: Mechanisms of TCM compounds in the treatment of psoriasis by regulating NF-κB signaling pathway

TCM compound	Mechanism	Study
Nourishing Blood and Detoxifying Soup	[TNF-α、IL-6、IL-1β、IFN-γ、IL-17、IL-23、PCNA、Ki67、$CD4^+$、$CD8^+$] ↓， HSP70 ↓， TLR4/NF-κB ↓	[66]
Dan Shen Bai Bi Xiao	[TNF-α、IL-17A、IL-23、IL-6、IL-1β、IL-22] ↓，[NF-κB、STAT3、MAPKs] ↓	[68]
Xiao Yin Jie Du Granules	[K6、K16、K17、IL-36γ、IL-17、IL-22、$CD4^+$T] ↓，[S1PR1-5、NF-κB p65、p- NF-κB p65、IKKα、p- IKKα] ↓， Th17 ↓	[70]

5. Summary and Prospects

Currently, the incidence of psoriasis is extremely high, and its pathogenesis is not yet fully understood. There is no completely curative treatment available domestically or internationally, hence the ongoing

exploration of new therapeutic methods for psoriasis is an urgent task in the medical research community. The NF-κB signaling pathway is a complex network that is influenced by a variety of upstream and downstream mediators and plays a key role in inflammatory responses and immune responses in diseases. Modulating various components of the NF-κB signaling pathway can significantly improve psoriasis and represents a novel targeted pathway for its treatment. Traditional Chinese medicine (TCM) has always been a treasure trove of knowledge for exploring the treatment of various diseases, with its multi-faceted, multi-targeted, broad-spectrum effects and fewer adverse reactions, it plays a unique role in the treatment of psoriasis. Based on this, a summary of the regulation of the NF-κB signaling pathway by Chinese medicinal monomers and compound formulas in treating psoriasis is provided, which helps to further explore the mechanism of NF-κB signaling pathway regulation in psoriasis and provides scientific evidence for the treatment of psoriasis with TCM.

In summary, this article has discussed the NF-κB signaling pathway and its role in the pathogenesis of psoriasis and has summarized how various Chinese medicinal monomers, active ingredients, and compound formulas can improve psoriasis by directly or indirectly acting on the NF-κB signaling pathway. It is not difficult to see that as a classical inflammatory signaling pathway, the inhibition of NF-κB by Chinese medicinal monomers, active ingredients, and compound formulas can downregulate psoriasis-related inflammatory cytokines. It can also regulate the expression levels of genes or proteins related to psoriasis, such as T cells, macrophages, KCs, iNOS, COX-2, HO-1, NLRP3, etc., thereby playing roles in reducing inflammatory responses, inhibiting cell proliferation, regulating immunity, and controlling oxidative stress to improve psoriasis. In addition, while regulating the NF-κB signaling pathway, other pathways such as STAT, MAPK, Nrf2, Akt, PI3K, etc., can also be regulated in a network to better exert their therapeutic effects on psoriasis.

From the current research findings on the regulation of the NF-κB signaling pathway by TCM in the treatment of psoriasis, there are still some shortcomings: (1) The NF-κB signaling pathway can interact with multiple pathways, and the mechanisms by which different signaling pathways affect psoriasis are not yet fully understood; (2) The research methods mainly focus on animal experiments and in vitro cell experiments, lacking corresponding clinical studies; (3) Most of the research is on Chinese medicine, and there is a lack of exploration of the modern molecular mechanisms of characteristic TCM therapies. Therefore, future research should delve deeper to further clarify the mechanisms by which various signaling pathways interact and collectively affect psoriasis; based on improved experimental research, the development of related Chinese patent medicines can be initiated, and gradually put into large-scale, multi-centered clinical trial studies to verify their efficacy and safety; at the same time, actively explore the mechanism of characteristic TCM therapies to provide more effective methods for the clinical treatment of psoriasis.

References

[1] GRIFFITHS C E M, ARMSTRONG A W, GUDJONSSON J E, et al. Psoriasis [J]. Lancet, 2021, 397(10281): 1301-15.

[2] ROSZKIEWICZ M, DOPYTALSKA K, SZYMAŃSKA E, et al. Environmental risk factors and epigenetic alternations in psoriasis [J]. Ann Agric Environ Med, 2020, 27(3): 335-42.

[3] DAND N, MUCHA S, TSOI L C, et al. Exome-wide association study reveals novel psoriasis susceptibility locus at TNFSF15 and rare protective alleles in genes contributing to type I IFN signalling [J]. Hum Mol Genet, 2017, 26(21): 4301-13.

[4] MAHIL S K, SMITH C H. Psoriasis biologics: a new era of choice [J]. Lancet, 2019, 394(10201): 807-8.

[5] Li H X, Hu L, Zheng Y, et al. Epidemiological burden of psoriasis in China based on Global Burden of disease (GBD) big data [J]. Chin J Dermatovenereology, 2021, 35(04): 386-92.
[6] KORMAN N J. Management of psoriasis as a systemic disease: what is the evidence? [J]. Br J Dermatol, 2020, 182(4): 840-8.
[7] SŁUCZANOWSKA-GŁABOWSKA S, SALMANOWICZ M, STANISZEWSKA M, et al. The Role of Sirtuins in the Pathogenesis of Psoriasis [J]. Int J Mol Sci, 2023, 24(13).
[8] YU J, ZHAO Q, WANG X, et al. Pathogenesis, multi-omics research, and clinical treatment of psoriasis [J]. J Autoimmun, 2022, 133: 102916.
[9] GUO J, ZHANG H, LIN W, et al. Signaling pathways and targeted therapies for psoriasis [J]. Signal Transduct Target Ther, 2023, 8(1): 437.
[10] VAN DE KERKHOF P C. From Empirical to Pathogenesis-Based Treatments for Psoriasis [J]. J Invest Dermatol, 2022, 142(7): 1778-85.
[11] ZHU C, CHEN Y, TAI Z, et al. Effect and mechanism of longkui yinxiao soup in treating psoriasis in mice [J]. Front Pharmacol, 2023, 14: 1136604.
[12] SHISHODIA S. Molecular mechanisms of curcumin action: gene expression [J]. Biofactors, 2013, 39(1): 37-55.
[13] LIU P, LI Y, WANG W, et al. Role and mechanisms of the NF-κB signaling pathway in various developmental processes [J]. Biomed Pharmacother, 2022, 153: 113513.
[14] ALHARBI K S, FULORIA N K, FULORIA S, et al. Nuclear factor-kappa B and its role in inflammatory lung disease [J]. Chem Biol Interact, 2021, 345: 109568.
[15] KUSIAK A, BRADY G. Bifurcation of signalling in human innate immune pathways to NF-κB and IRF family activation [J]. Biochem Pharmacol, 2022, 205: 115246.
[16] AHMAD S, ABBAS M, ULLAH M F, et al. Long non-coding RNAs regulated NF-κB signaling in cancer metastasis: Micromanaging by not so small non-coding RNAs [J]. Semin Cancer Biol, 2022, 85: 155-63.
[17] GULEI D, DRULA R, GHIAUR G, et al. The Tumor Suppressor Functions of Ubiquitin Ligase KPC1: From Cell-Cycle Control to NF-κB Regulator [J]. Cancer Res, 2023, 83(11): 1762-7.
[18] MUSSBACHER M, DERLER M, BASÍLIO J, et al. NF-κB in monocytes and macrophages - an inflammatory master regulator in multitalented immune cells [J]. Front Immunol, 2023, 14: 1134661.
[19] WANG Y, YE R, FAN L, et al. A TNF-α blocking peptide that reduces NF-κB and MAPK activity for attenuating inflammation [J]. Bioorg Med Chem, 2023, 92: 117420.
[20] BRÁS J P, BRAVO J, FREITAS J, et al. TNF-alpha-induced microglia activation requires miR-342: impact on NF-κB signaling and neurotoxicity [J]. Cell Death Dis, 2020, 11(6): 415.
[21] MCINTOSH K, KHALAF Y H, CRAIG R, et al. IL-1β stimulates a novel, IKKα -dependent, NIK -independent activation of non-canonical NFκB signalling [J]. Cell Signal, 2023, 107: 110684.
[22] SOMENSI N, RABELO T K, GUIMARÃES A G, et al. Carvacrol suppresses LPS-induced pro-inflammatory activation in RAW 264.7 macrophages through ERK1/2 and NF-κB pathway [J]. Int Immunopharmacol, 2019, 75: 105743.
[23] GULDENPFENNIG C, TEIXEIRO E, DANIELS M. NF-κB's contribution to B cell fate decisions [J]. Front Immunol, 2023, 14: 1214095.
[24] GUO Q, JIN Y, CHEN X, et al. NF-κB in biology and targeted therapy: new insights and translational implications [J]. Signal Transduct Target Ther, 2024, 9(1): 53.
[25] YU H, LIN L, ZHANG Z, et al. Targeting NF-κB pathway for the therapy of diseases: mechanism and clinical study [J]. Signal Transduct Target Ther, 2020, 5(1): 209.
[26] MITCHELL J P, CARMODY R J. NF-κB and the Transcriptional Control of Inflammation [J]. Int Rev Cell Mol Biol, 2018, 335: 41-84.
[27] BOCHEŃSKA K, SMOLIŃSKA E, MOSKOT M, et al. Models in the Research Process of Psoriasis [J]. Int J Mol Sci, 2017, 18(12).

[28] ZHANG P, SU Y, LI S, et al. The roles of T cells in psoriasis [J]. Front Immunol, 2023, 14: 1081256.
[29] ZHOU X, CHEN Y, CUI L, et al. Advances in the pathogenesis of psoriasis: from keratinocyte perspective [J]. Cell Death Dis, 2022, 13(1): 81.
[30] KAMATA M, TADA Y. Dendritic Cells and Macrophages in the Pathogenesis of Psoriasis [J]. Front Immunol, 2022, 13: 941071.
[31] GOLDMINZ A M, AU S C, KIM N, et al. NF-κB: an essential transcription factor in psoriasis [J]. J Dermatol Sci, 2013, 69(2): 89-94.
[32] RUAN Q, KAMESWARAN V, ZHANG Y, et al. The Th17 immune response is controlled by the Rel-RORγ-RORγ T transcriptional axis [J]. J Exp Med, 2011, 208(11): 2321-33.
[33] ZHU H, LOU F, YIN Q, et al. RIG-I antiviral signaling drives interleukin-23 production and psoriasis-like skin disease [J]. EMBO Mol Med, 2017, 9(5): 589-604.
[34] REBHOLZ B, HAASE I, ECKELT B, et al. Crosstalk between keratinocytes and adaptive immune cells in an IkappaBalpha protein-mediated inflammatory disease of the skin [J]. Immunity, 2007, 27(2): 296-307.
[35] SAKURAI K, DAINICHI T, GARCET S, et al. Cutaneous p38 mitogen-activated protein kinase activation triggers psoriatic dermatitis [J]. J Allergy Clin Immunol, 2019, 144(4): 1036-49.
[36] SUZUKI K, SUZUKI K, YABE Y, et al. NF-κB1 Contributes to Imiquimod-Induced Psoriasis-Like Skin Inflammation by Inducing Vγ4(+)Vδ4(+)γδT17 Cells [J]. J Invest Dermatol, 2022, 142(6): 1639-49.e5.
[37] LUO Y, RU Y, SUN X, et al. Characteristics of psoriasis vulgaris in China: a prospective cohort study protocol [J]. Ann Transl Med, 2019, 7(22): 694.
[38] ZOU J, GAO P, HAO X, et al. Recent progress in the structural modification and pharmacological activities of ligustrazine derivatives [J]. Eur J Med Chem, 2018, 147: 150-62.
[39] JIANG R, XU J, ZHANG Y, et al. Ligustrazine alleviates psoriasis-like inflammation through inhibiting TRAF6/c-JUN/NFκB signaling pathway in keratinocyte [J]. Biomed Pharmacother, 2022, 150: 113010.
[40] ZHANG L, WEI W. Anti-inflammatory and immunoregulatory effects of paeoniflorin and total glucosides of paeony [J]. Pharmacol Ther, 2020, 207: 107452.
[41] BAI X, YU C, YANG L, et al. Anti-psoriatic properties of paeoniflorin: suppression of the NF-kappaB pathway and Keratin 17 [J]. Eur J Dermatol, 2020, 30(3): 243-50.
[42] WANG D, CHEN J, PU L, et al. Galangin: A food-derived flavonoid with therapeutic potential against a wide spectrum of diseases [J]. Phytother Res, 2023, 37(12): 5700-23.
[43] SANGARAJU R, ALAVALA S, NALBAN N, et al. Galangin ameliorates Imiquimod-Induced psoriasis-like skin inflammation in BALB/c mice via down regulating NF-κB and activation of Nrf2 signaling pathways [J]. Int Immunopharmacol, 2021, 96: 107754.
[44] WANG Z F, LIU J, YANG Y A, et al. A Review: The Anti-inflammatory, Anticancer and Antibacterial Properties of Four Kinds of Licorice Flavonoids Isolated from Licorice [J]. Curr Med Chem, 2020, 27(12): 1997-2011.
[45] GUO D, WANG Q, LI A, et al. Liquiritin targeting Th17 cells differentiation and abnormal proliferation of keratinocytes alleviates psoriasis via NF-κB and AP-1 pathway [J]. Phytother Res, 2024, 38(1): 174-86.
[46] WU Y, CHEN X, GE X, et al. Isoliquiritigenin prevents the progression of psoriasis-like symptoms by inhibiting NF-κB and proinflammatory cytokines [J]. J Mol Med (Berl), 2016, 94(2): 195-206.
[47] YANG S J, WANG J J, CHENG P, et al. Ginsenoside Rg1 in neurological diseases: From bench to bedside [J]. Acta Pharmacol Sin, 2023, 44(5): 913-30.
[48] SHI Q, HE Q, CHEN W, et al. Ginsenoside Rg1 abolish imiquimod-induced psoriasis-like dermatitis in BALB/c mice via downregulating NF-κB signaling pathway [J]. J Food Biochem, 2019, 43(11): e13032.

[49] YANG S, LIU J, JIAO J, et al. Ar-Turmerone Exerts Anti-proliferative and Anti-inflammatory Activities in HaCaT Keratinocytes by Inactivating Hedgehog Pathway [J]. Inflammation, 2020, 43(2): 478-86.
[50] LI Y L, DU Z Y, LI P H, et al. Aromatic-turmerone ameliorates imiquimod-induced psoriasis-like inflammation of BALB/c mice [J]. Int Immunopharmacol, 2018, 64: 319-25.
[51] PERIFERAKIS A, PERIFERAKIS K, BADARAU I A, et al. Kaempferol: Antimicrobial Properties, Sources, Clinical, and Traditional Applications [J]. Int J Mol Sci, 2022, 23(23).
[52] LIU C, LIU H, LU C, et al. Kaempferol attenuates imiquimod-induced psoriatic skin inflammation in a mouse model [J]. Clin Exp Immunol, 2019, 198(3): 403-15.
[53] JAVED M, SALEEM A, XAVERIA A, et al. Daphnetin: A bioactive natural coumarin with diverse therapeutic potentials [J]. Front Pharmacol, 2022, 13: 993562.
[54] GAO J, CHEN F, FANG H, et al. Daphnetin inhibits proliferation and inflammatory response in human HaCaT keratinocytes and ameliorates imiquimod-induced psoriasis-like skin lesion in mice [J]. Biol Res, 2020, 53(1): 48.
[55] HUANG L, KIM M Y, CHO J Y. Immunopharmacological Activities of Luteolin in Chronic Diseases [J]. Int J Mol Sci, 2023, 24(3).
[56] ZHOU W, HU M, ZANG X, et al. Luteolin attenuates imiquimod-induced psoriasis-like skin lesions in BALB/c mice via suppression of inflammation response [J]. Biomed Pharmacother, 2020, 131: 110696.
[57] WEN Y, WANG Y, ZHAO C, et al. The Pharmacological Efficacy of Baicalin in Inflammatory Diseases [J]. Int J Mol Sci, 2023, 24(11).
[58] WU X, DENG X, WANG J, et al. Baicalin Inhibits Cell Proliferation and Inflammatory Cytokines Induced by Tumor Necrosis Factor α (TNF-α) in Human Immortalized Keratinocytes (HaCaT) Human Keratinocytes by Inhibiting the STAT3/Nuclear Factor kappa B (NF-κB) Signaling Pathway [J]. Med Sci Monit, 2020, 26: e919392.
[59] LIU A, ZHANG B, ZHAO W, et al. Catalpol ameliorates psoriasis-like phenotypes via SIRT1 mediated suppression of NF-κB and MAPKs signaling pathways [J]. Bioengineered, 2021, 12(1): 183-95.
[60] CHEN H, LU C, LIU H, et al. Quercetin ameliorates imiquimod-induced psoriasis-like skin inflammation in mice via the NF-κB pathway [J]. Int Immunopharmacol, 2017, 48: 110-7.
[61] YANG Y, ZHANG Y, CHEN X, et al. Khasianine ameliorates psoriasis-like skin inflammation and represses TNF-α/NF-κB axis mediated transactivation of IL-17A and IL-33 in keratinocytes [J]. J Ethnopharmacol, 2022, 292: 115124.
[62] CHEN H, WANG C, TANG B, et al. P. granatum Peel Polysaccharides Ameliorate Imiquimod-Induced Psoriasis-Like Dermatitis in Mice via Suppression of NF-κB and STAT3 Pathways [J]. Front Pharmacol, 2021, 12: 806844.
[63] Zhou Mingming. Effects of shikonin on NF-κB signaling pathway and related inflammatory factors in imiquimod-induced psoriasis mice model [D]; China Medical University, 2022.
[64] Wang Mei, Meng Nana, Wen Yijie, et al. Naringin inhibits lipopolysaccharide induced inflammatory response in HaCaT cells through P38 MAPK/NF-κB pathway [J]. Drug Evaluation Research, 2019, 42(06): 1081-6.
[65] LU Jing-jing, HAN Xiao-li, SUN Wen-wen, et al. Clinical observation of Yangxue-Jiedu decoction combined with traditional Chinese medicine bath in the treatment of blood-drying psoriasis. Chin J Traditional Chinese Medicine, 2021, 36(07): 4405-7.
[66] LV J, WANG Y, XU J, et al. Protective effect of Yangxue Jiedu Soup against psoriasis-like lesions by regulating TLR4/NF-κB signaling pathway mediated by secretion of exosome HSP70 [J]. Biomed Pharmacother, 2022, 147: 112604.
[67] Jin Xiaoqi. Study on the therapeutic effect of Danshenbai 疙 Xiao pills on psoriasis [D]; Hubei University of Traditional Chinese Medicine, 2020.

[68] JIN X, XU H, HUANG C, et al. A Traditional Chinese Medicine Formula Danshen Baibixiao Ameliorates Imiquimod-Induced Psoriasis-Like Inflammation in Mice [J]. Front Pharmacol, 2021, 12: 749626.

[69] ZHANG Runtian, Chen Xi, Huo Chunbo, et al. Effect of Xiaoyin Jiedu granule on Jurkat cell abnormal proliferation model [J]. Chinese Journal of Traditional Chinese Medicine, 2017, 58(12): 1049-52.

[70] WANG Z, ZHANG G, ZHANG H, et al. Xiaoyin Jiedu Granules may alleviate psoriasis-like skin diseases in mice by regulating sphingosine 1-phosphate receptor expression and reducing Th17 cells [J]. Heliyon, 2023, 9(8): e19109.