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Herbal Modulators of JAK/STAT Signalling in Chronic Inflammatory and Autoimmune Disorders: An Integrative Approach

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Abstract

Background: Janus kinase/signal transducer and activator of transcription (JAK/STAT) is a key signaling protocol operating in the regulation of immune cells, cytokine communication and inflammation. The JAK/STAT pathway has been implicated in the pathogenesis of several chronic inflammatory and autoimmune diseases, including Rheumatoid Arthritis (RA), psoriasis, Inflammatory Bowel Disease (IBD), and Systemic Lupus Erythematosus (SLE). While pharmacological JAK inhibitors (e.g., tofacitinib, ruxolitinib) have shown therapeutic efficacy, their long-term use is often limited by adverse effects, high costs, and immunosuppressive risks. Over the last few years, a growing body of evidence has highlighted the potential of herbal formulations and plant-derived bioactive compounds as safe, effective, and multi-target modulators of the JAK/STAT pathway. Phytochemicals (curcumin, resveratrol, berberine, and andrographolide) have been observed to affect key actors of this pathway (by inhibiting JAK kinases, STAT activation, and upstream proinflammatory cytokines downregulation). **Aim:** The aim is to systematically explore the molecular mechanisms of herbal modulators acting on JAK/STAT signalling, their relevance in disease-specific contexts, and the evidence from preclinical and clinical studies. The review dwells on the new methods that are being developed to comprehend the polypharmacological aspect of such compounds, such as network pharmacology, systems biology, and molecular docking. **Result:** Integrating herbal therapeutics into JAK/STAT-targeted strategies offers a promising complementary approach to conventional therapies. Nevertheless, more clinical research and standardisation of the composition, as well as safety profiling, are required to confirm their usage in treatment. **Conclusion:** The present integrative review will inform future research, which would aim at the utilisation of herbal bioactives in the chronic inflammatory and autoimmune disease management using JAK/STAT modulation.

Major Findings: The modulation of JAK/STAT signalling pathway by inhibiting JAK phosphorylation, suppressing the expression of pro-inflammatory cytokines and regulating the activation of STAT occurs with herbal compounds containing curcumin, withaferin A and berberine, which suppress pro-inflammatory cytokines and modulate JAK/STAT signalling pathway in autoimmune and inflammatory disorders. In spite of positive data in preclinical studies, M-T effect and even despite multi-targeting effects of their therapeutic properties, standardised clinical trials and also pharmacokinetic studies should be continued to integrate them into the repertoire of mainstream immunotherapies.

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1. Introduction

The group of debilitating conditions consists of chronic inflammatory and autoimmune disorders, including Rheumatoid Arthritis (RA), psoriasis, Inflammatory Bowel Disease (IBD), and Systemic Lupus Erythematosus (SLE), which are typified by long-standing immune activation and tissue destruction. Such conditions are frequently complex with cross-immunopathological features such as excess of proinflammatory cytokines, T cell-activation malfunctions, and immune-tolerance disfunctions[1]. Despite their diverse clinical presentations, a common molecular hallmark in many of these conditions is the dysregulation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling pathway.

JAKSTAT pathway is a key intracellular signalling cascade that transmits the signal of cytokine receptors to the nucleus, affecting gene expression pertaining to the proliferation, differentiation and cytokine production of immune cells. Overactive activation of this pathway has been linked to the pathogenesis of several autoimmune and inflammatory diseases, in which it is implicated in chronic inflammation and immune-mediated cell or tissue damage[2]. Consequently, selective inhibition of JAK family kinases (JAK1, JAK2, JAK3, TYK2) has emerged as a promising therapeutic strategy, and several small-molecule JAK inhibitors (e.g., tofacitinib, baricitinib, ruxolitinib) have been developed and approved for clinical use.

Nevertheless, synthetic JAK inhibitors possess a set of shortcomings, such as the enhanced possibility of infections, thrombosis, lipid disorders, and high costs of treatment, which might result in the impossibility of using them comprehensively. This has created interest in safer and economical alternatives, preferably of natural origins[3]. Herbal medicines and phytochemicals have been traditionally used for centuries to modulate immune responses and inflammation. The recent scientific studies have started decoding their possible potential in regulating molecular signalling pathways, such as JAK/STAT, in multi-targeted ways with fewer side effects.

Given the growing body of evidence supporting the immunomodulatory effects of plant-derived compounds, there is a compelling rationale to explore their role as modulators of the JAK/STAT pathway in autoimmune and inflammatory disorders[4]. This review seeks to present an integrative review of some of the major herbal bioactives and formulations known to modulate JAK/STAT signalling. It studies their molecular specifics, references to specific diseases, preclinical and clinical data on them, as well as briefly focuses attention on new tools like network pharmacology and systems biology that reveal the specifics of their therapeutic properties. The overarching goal is to highlight the promise of herbal interventions as adjuncts or alternatives to conventional JAK inhibitors in managing chronic inflammatory and autoimmune conditions[5].

2. JAK/STAT Signalling Pathway: A Molecular Overview

2.1 Core Components of the JAK/STAT Pathway

The JAK/STAT pathway mainly comprises two groups of proteins, namely Janus kinases (JAKs) and Signal Transducers and Activators of Transcription (STATs). The JAKs are four in number and include JAK1, JAK2, JAK3 and TYK2, each of which is coupled with particular cytokine receptors and cellular activities[6]. JAK1 and JAK2 are ubiquitously expressed and mediate signalling for various proinflammatory and growth-related cytokines. JAK3 is mainly present within the hematopoietic cells and associates with the common gamma chain (γc) in interleukin signal transmission, including IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21. TYK2 intervenes in type I interferons, IL-12 and IL-23 propagation.

The STAT family includes seven members: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6. These transcription factors are induced in the downstream signalling of JAKs, and they aid in the transcription of genes related to cell survival, proliferation, differentiation, and immune responses.

Selectivity in JAKs and STATs pair determines the cell response to the external stimuli[7].

2.2 Mechanism of JAK/STAT Activation

The process of activation of the JAK/STAT pathway starts with the action of a cytokine or a growth factor upon the cell surface. It will result in receptor dimerisation and the consequent activation of the linked JAKs through trans-phosphorylation. Activated JAKs then phosphorylate specific tyrosine residues on the cytoplasmic domains of the receptor, creating docking sites for STAT proteins. Once recruited, STATs are themselves phosphorylated by JAKs, enabling their dimerization[8]. The activated STAT dimers are then translocated to the nucleus, where they bind with DNA response elements and mediate transcription of target genes. It is a faster and more direct process, which enables cells to respond easily to external stimuli.

2.3 Role in Immune Cell Regulation and Cytokine Signalling

The JAK/STAT pathway constitutes the most crucial regulator of immune response by coordinating the communication of various cytokines and growth factors implicated in inflammation and hematopoiesis. STAT1 plays a very important role in interferon-initiated reactions, and it is related to the differentiation of Th1 cells[9]. STAT3 promotes Th17 cell development and plays a role in the maintenance of inflammation, while STAT4 and STAT6 are involved in Th1 and Th2 differentiation, respectively. The role of STAT5 is critical in the signalling of IL-2 and the growth hormone, in the determination of T-cell proliferation and survival.

This pathway also modulates the production of various cytokines, chemokines, and adhesion molecules, thereby regulating immune cell trafficking, activation, and effector functions. These self-renewal mechanisms, through the JAK/STAT pathway, help not only to promote host-defence but also help in immune homeostasis[10].

2.4 Dysregulation in Autoimmune and Inflammatory Diseases

Dysregulated functioning of JAK/STAT signalling is linked to the aetiology of numerous autoimmune and chronic inflammatory disorders. During rheumatoid

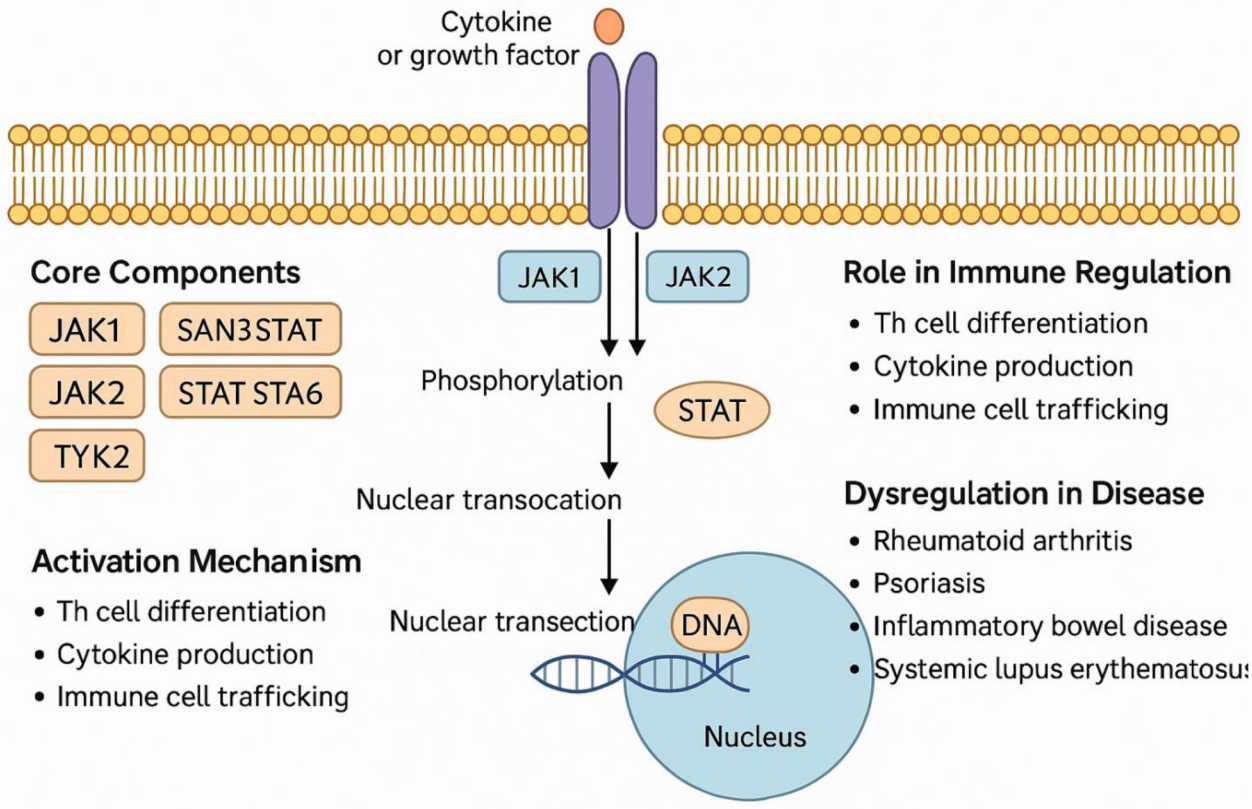


Figure 1. Canonical JAK/STAT signalling pathway.

arthritis, heightened activation of STAT3 facilitates the survival and growth of fibroblast-like synoviocytes as well as augments the Th17 -mediated inflammation. In psoriasis, the IL-23/IL-17 axis, largely mediated via STAT3, drives keratinocyte hyperproliferation and neutrophilic infiltration[11]. Chronic dysfunction of the epithelial barrier occurs, which has been attributed to chronic levels of activated STAT1 and STAT3 in inflammatory bowel disease. In a parallel fashion, hyperactive signalling of type I interferons in the pathogenesis of systemic lupus erythematosus causes a variety of problems, including autoantibody synthesis and chronic immune stimulation, by overactivation of JAK1, TYK2 and STAT1[12].

The widespread involvement of JAK/STAT dysregulation in various immune-mediated diseases underscores its importance as a therapeutic target. Although synthetic JAK inhibitors have proved effective, their drawbacks are such that it is prudent to use alternative methods to target this pathway, one of which involves using herbal compounds to affect the pathway via varied mechanisms of action (Figure 1).

3. Herbal Modulation of JAK/STAT Pathway: Mechanistic Insights

3.1 Direct Inhibition of JAK Kinases

Other herbal bioactives have been shown to be able to directly inhibit JAK kinases by blocking their phosphorylation, thus inhibiting downstream activation through STAT. Curcumin, derived from *Curcuma longa,* has also proven to inhibit JAK1 and JAK2 in many inflammation models, resulting in inhibited cytokine signaling[13]. Similarly, berberine, an alkaloid from *Berberis vulgaris*, has been found to suppress JAK2 phosphorylation, contributing to its anti-inflammatory and anti-arthritic effects. The significant active constituent of *Andrographis paniculata* is Andrographolide, which suppresses JAK1 and TYK2, and therefore interferes with the signalling activities of IFN-gamma and IL-6. Such phytochemicals perform their effect by binding to the ATP binding pockets of JAKs or blocking the structural rearrangements that activate the JAKs and cannot be considered as a synthetic JAK blocker, as it has fewer side effects compared to synthetic JAK blockers[14].

3.2 Regulation of STAT Activation and Nuclear Translocation

Besides the JAKs inhibition, herbal compounds also impair the activation and nuclear translocation of the STAT proteins in general, or at least of the STAT1 and STAT3, known to play major parts in the inflammatory and autoimmune reactions. Resveratrol, a polyphenol found in grapes and berries, is known to inhibit STAT3 phosphorylation and its subsequent dimerisation and nuclear translocation, which suppresses pro-inflammatory gene expression[15]. The major green tea Epigallocatechin Gallate (EGCG) was reported to inhibit the expression of inducible nitric oxide synthase (iNOS) and TNF-alpha, through downregulating the transcription factor STAT1 and STAT3 in different immune cells. Inhibiting the activation of STAT and nuclear activity in the body, these herbs are actually effective in overcoming chronic inflammations and overactions of the immune system[16].

3.3 Modulation of Upstream Cytokines (IL-6, IFN-γ, IL-23, etc.)

The other important way through which herbs can regulate the JAK/STAT pathway is by reducing the synthesis of upstream cytokines that trigger the pathway. As an example, the *Tinospora cordifolia* extracts have been known to reduce IL-6 and IFN-levels and consequently JAK/STAT signalling. Baicalin, derived from *Scutellaria baicalensis*, modulates IL-17 and IL-23 expression, leading to suppression of Th17-mediated responses in autoimmune disorders[17]. Such activities emphasise the upstream regulative prospects of herbal formulations to depressed cytokine storms and harmed illness pathophysiology in immune-mediated disorders.

3.4 Cross-talk with Other Pathways (NF-κB, MAPK, PI3K/Akt)

Sometimes herbal JAK/STAT modulators have their actions through multi-pathway interactions, and show cross-talk activities with key inflammatory pathways like NF-κB, MAPK, and PI3K/Akt. For example, curcumin inhibits both STAT3 and NF-κB activation, offering dual suppression of inflammatory gene transcription. Berberine concurrently inhibits MAPK and PI3K/Akt pathways, contributing to broader

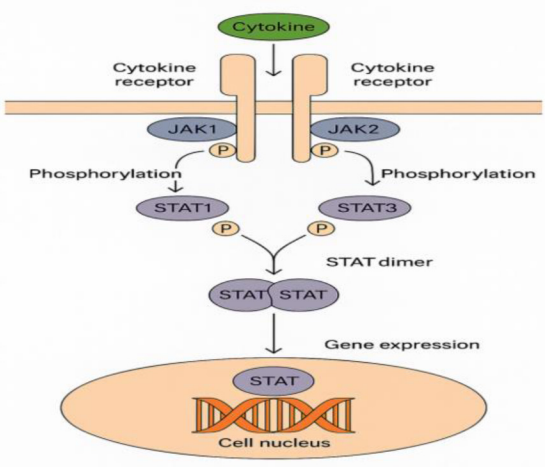


Figure 2. Herbal modulatory sites within the JAK/STAT signalling cascade.

anti-inflammatory efficacy[18]. The noted interactions highlight the systems-level consequences of herbal derivatives and their prospects as polypharmacological entities. The therapeutic usefulness of modulating several signalling cascades is increased, and it is the reason to incorporate them into a complex intervention plan in order to manage the disease (Figure 2).

4. Key Herbal Candidates and Phytochemicals

Several medicinal plants and their bioactive phytoconstituents have been found to regulate the JAK/STAT signalling pathway, directly or indirectly, by means of a multiplicity of mechanisms. These herbal contenders have been extensively explored in preclinical models of the autoimmune as well as chronic inflammatory diseases[19]. This section highlights the most promising herbs and their active compounds, with emphasis on their molecular targets, immunopharmacological actions, and relevance to JAK/STAT modulation.

4.1 *Curcuma longa* (Curcumin)

The most studied anti-inflammatory compound is curcumin (principal curcuminoid in *Curcuma longa* (turmeric)). It inhibits phosphorylation of STAT3, disrupts IL-6 and IL-1β in different immune cells. Curcumin strongly inhibited the process of differentiation and production of Th17 cells in models of rheumatoid arthritis and colitis ulcerative[20]. Cardamom and curcumin have also been shown to inhibit upstream kinases such as JAK1 and JAK2, thus a potent regulating mechanism of the IL-6/JAK/STAT3 axis.

4.2 *Withania somnifera* (Withanolides)

The immunomodulatory and anti-inflammatory properties of withanolides, steroidal lactones present in *Withania somnifera* (Ashwagandha), have been observed. One of its biggest constituents, Withaferin A, suppresses the activation of STAT3 and lowers the IL-6, TNF-alpha, and IFN-gamma levels in T cells and macrophages. It also induces apoptosis of disease-causing immune cells but maintains regulatory T cells, consequently restoring the balanced condition of the immune system in autoimmune diseases[21].

4.3 *Berberis vulgaris* (Berberine)

Berberine is an isoquinoline alkaloid that is found in *Berberis vulgaris,* and it blocks the phosphorylation of JAK2 and STAT3 in several disease models, such as the inflammatory bowel disease and systemic lupus erythematosus disease models. It has similarly been known to suppress the activation of IL-23 mediated activation of STAT3 cells in Th17 cells. It is multi-targeted and works on MAPK and AMPK pathways, which further increases its therapeutic profile[22].

4.4 *Andrographis paniculata* (Andrographolide)

The *Andrographis paniculata,* diterpenoid andrographolide, has been traditionally used in Ayurvedic medicine and Chinese medicine. It prevents the phosphorylation of STAT3 and suppresses the IL-6 and IL-1b level. In experimental models of arthritis, andrographolide has proven useful in lowering inflammation of joints and hyperplasia synovials, through inhibition of the JAK1/STAT3 axis[23]. It also balances NF- kB and PI 3/Akt activities, which are part of its anti-inflammatory effects that show against a wide spectrum.

4.5 *Scutellaria baicalensis* (Baicalin and Baicalein)

Scutellaria baicalensis, Flavonoids Baicalin and baicalein have demonstrated potential in inhibiting IL-17, IL-23 and IFN-γ, which conferred STAT activation. These

substances suppress Th17 polarisation, and they boost regulatory T cell effects in autoimmune models. They also show neuroprotectivity through the suppression of microglial STAT1/3 signaling[24].

4.6 *Camellia sinensis* (EGCG)

The main catechin of green tea (*Camellia sinensis*), epigallocatechin-3-gallate (EGCG), is a strong antioxidant and immunomodulator. EGCG suppresses STAT1 and STAT3 activation and inhibits the production of IL-6, IL-12, and IFN-γ. It also alters activation of NF-κB thus having additive anti-inflammatory effects[25]. EGCG has been tested on models of multiple sclerosis, colitis and lupus.

4.7 *Vitis vinifera* (Resveratrol)

Polyphenolic resveratrol, which is present in grapes and berries (*Vitis vinifera*) has been shown to prevent phosphorylation and nuclear translocation of STAT3[26]. It is also able to downregulate the inflammatory cytokines like IL-6, TNF-α and IL-1β. Resveratrol enhances autophagy and reduces oxidative stress, making it particularly effective in neuroinflammatory and metabolic autoimmune disorders (Table 1).

5. Disease-specific Evidence

5.1 Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is a long-term, autoimmune disorder in which the joints of the patient become inflamed and, consequently, undergo the cartilage destruction process. An intrinsic pathogenic axis in RA is the IL-6/JAK/ STAT3 pathway, and this mediates synovial hyperplasia, angiogenesis, and production of inflammatory cytokines. Herbal interventions have shown promise in attenuating this pathway. *Withania somnifera* (Ashwagandha) contains withanolides that downregulate IL-6 and STAT3 expression, leading to decreased synovial inflammation. *Boswellia serrata*, containing high levels of boswellic acids, is anti-inflammatory and has been reported to inhibit the JAK/STAT-mediated cytokine production in arthritic animal cancer models[27]. Curcumin, a plant of *Curcuma longa*, works through the effects of JAK1 and STAT3 phosphorylation and inhibition of Th17 differentiation, according to which it has the strongest effect on protecting the joints and relieving RA symptoms.

5.2 Psoriasis

Psoriasis is an immune-mediated, chronic skin disease whose pathogenesis depends mainly on STAT3-mediated activation of Th17 cells and keratinocyte proliferation. The increased level of IL-23 and IL-17 triggers the NF-κB and activation of the JAK/STAT signal, especially in STAT3 activation in the lesional skin. Herbal alternatives have indicated promising effects in the tapering of this axis. Aloe vera gel, commonly used topically, demonstrates STAT3 inhibition and improves epidermal barrier function[28]. The *Curcuma longa* has been identified to suppress the

Table 1. Key Herbal Modulators of the JAK/STAT Pathway

Herbal Source	Active Constituent(s)	Mechanism of JAK/STAT Modulation	Therapeutic Relevance
Curcuma longa	Curcumin	Inhibits JAK1/JAK2, STAT3 phosphorylation; downregulates IL-6, IL-1β	Rheumatoid arthritis, ulcerative colitis
Withania somnifera	Withaferin A, Withanolides	Inhibits STAT3 activation; suppresses IL-6, TNF-α, IFN-γ	Autoimmune arthritis, immune hyperactivation
Berberis vulgaris	Berberine	Inhibits JAK2/STAT3; blocks IL-23-induced Th17 polarization	Lupus, IBD, inflammatory diseases
Andrographis paniculata	Andrographolide	Suppresses JAK1/STAT3 and proinflammatory cytokines	Arthritis, psoriasis, systemic inflammation
Scutellaria baicalensis	Baicalin, Baicalein	Inhibits STAT1/STAT3; reduces IL-17/IL-23 axis	Multiple sclerosis, SLE, allergic inflammation
Camellia sinensis	EGCG	Inhibits STAT1/STAT3; suppresses IL-6, IFN-γ, NF-κB	Lupus, multiple sclerosis, colitis
Vitis vinifera	Resveratrol	Blocks STAT3 phosphorylation and nuclear translocation	Neuroinflammation, metabolic disorders, and arthritis

IL-17 and IL-22 signalling by disrupting the pattern of activity of STAT3 and NF-κB. Furthermore, *Tinospora cordifolia,* which is an immunoregulating agent, inhibited the Th17 responses as well as STAT signalling in psoriatic inflammation-using models.

5.3 Inflammatory Bowel Disease (IBD)

IBD (comprising Crohn disease and ulcerative colitis) is characterised by persistent inflammation along the gastrointestinal tract, and there are indications that one of its underlying causes could be excessively active JAK1/STAT1/STAT3 in intestinal epithelial cells and immune infiltrates. JAK inhibitors have shown considerable therapeutic efficacy in the preclinical study of colitis models[29]. Among herbal modulators, *Berberis vulgaris* (berberine) stands out for its ability to inhibit STAT3 phosphorylation and suppress IL-6, IL-17, and TNF-α production. *Boswellia serrata* extracts are traditionally used to treat gut inflammation, which arrests the object of inflammation-related markers of STAT. Due to its glycyrrhizin component, *Glycyrrhiza glabra* (liquorice) in addition to mucosal healing effects, has immunosuppressant effects through the JAK/STAT3 and PI3K / Akt pathways[30].

5.4 Systemic Lupus Erythematosus (SLE)

SLE is a paradigmatic systemic autoimmune disease with imbalanced B-cell responses and disseminated inflammation. One of the SLE pathogenesis signatures is the interferon-driven STAT1 and STAT2 activation that facilitates antibody production and immune complex deposition. Herbal immunosuppressants have shown potential in modulating this response. *Tripterygium wilfordii* (Thunder God Vine) has potent anti-inflammatory effects through the suppression of type I IFN signalling and STAT1 phosphorylation[31]. Likewise, green tea polyphenols, particularly EGCG of *Camellia sinensis*, inhibit the activity of STAT1 and STAT3 activation in dendritic cells and T lymphocytes. These natural products not only reduce the production of inflammatory cytokines but also enhance clinical outcomes of proteinuria and skin lesions in lupus susceptible models (Table 2).

6. Preclinical and Clinical Evidence

6.1 Summary of *In Vitro* and *In Vivo* Models

Much of the existing information regarding the herbal modulation of the JAK/STAT pathway relies on preclinical research findings by using *in vitro* cell models and *in vivo* animal models. *In vitro* studies using macrophages, dendritic cells and T lymphocytes demonstrated that the bioactive molecules, including curcumin, berberine and withaferin a downregulate inflammation via impairing phosphorylation of JAKs and STATs, downregulating the expression of inflammatory cytokines, including IL-6, IFN-γ, and TNF-α[32]. *In vivo* studies in murine models of rheumatoid arthritis, psoriasis, and colitis have demonstrated reduced disease severity upon treatment

Table 2. Herbal modulators of the JAK/STAT pathway in autoimmune and inflammatory disorders

Disease	Key JAK/STAT Target(s)	Herbal Interventions	Active Constituents	Mechanism of Action
Rheumatoid Arthritis (RA)	IL-6/JAK1/JAK2/STAT3	*Withania somnifera*, *Boswellia serrata*, *Curcuma longa*	Withaferin A, Boswellic acids, Curcumin	Inhibit IL-6 and STAT3 signaling; suppress Th17 differentiation
Psoriasis	IL-23/STAT3	*Aloe vera*, *Curcuma longa*, *Tinospora cordifolia*	Polysaccharides, Curcumin, Tinosporaside	Downregulate STAT3; reduce keratinocyte proliferation and IL-17/ IL-22 levels
Inflammatory Bowel Disease	JAK1/STAT1/STAT3	*B. vulgaris*, *Boswellia serrata*, *Glycyrrhiza glabra*	Berberine, Boswellic acids, Glycyrrhizin	Inhibit STAT3; reduce pro-inflammatory cytokines; enhance mucosal healing
Systemic Lupus Erythematosus (SLE)	IFN-α/TYK2/STAT1/STAT2	*Tripterygium wilfordii*, *Camellia sinensis*	Triptolide, EGCG	Suppress IFN signalling and STAT1/2; reduce autoantibody production

with these herbs, alongside suppressed activation of STAT1 and STAT3. These results are indicative of the use of herbal compounds as an immunomodulatory agent with the ability to block JAK/STAT-mediated pathogenesis[33].

6.2 Clinical Trial Data (If Available)

A number have been belied out to human trials, although few. As an illustration, clinical studies are performed on patients with rheumatoid arthritis and ulcerative colitis using *Curcuma longa* extracts that showed lower inflammatory markers and improved symptoms. *Withania somnifera* has been evaluated in small clinical settings for stress-related immune dysregulation, showing favourable effects on cytokine balance and safety. Berberine has demonstrated clinical efficacy in the treatment of metabolic syndrome and ulcerative colitis, but JAK/STAT regulation has not been adequately tested in humans yet[34]. All in all, there is a lack of clinical data, and strong, large-scale randomised controlled trials are required to confirm the preclinical data and identify whether the results can be adopted clinically.

6.3 Limitations of Current Herbal Research

Nevertheless, the herbal JAK/STAT modulator research field is marred by a number of shortcomings, notwithstanding the promising outcomes. To begin with, numerous studies use crude extracts without isolating any active constituents or determining their respective doses, thus becoming hard to replicate[35]. Second, the majority of mechanistic information concerns only *in vitro* conditions and *in vivo* studies frequently fail to provide translational measures. Moreover, no comparative studies have been done between herbal interventions and synthetic JAK inhibitors, which could explain the treatment worth of phytomedicines in reality. These gaps highlight the need for more focused pharmacological research, mechanistic elucidation, and comparative efficacy studies (Figure 3).

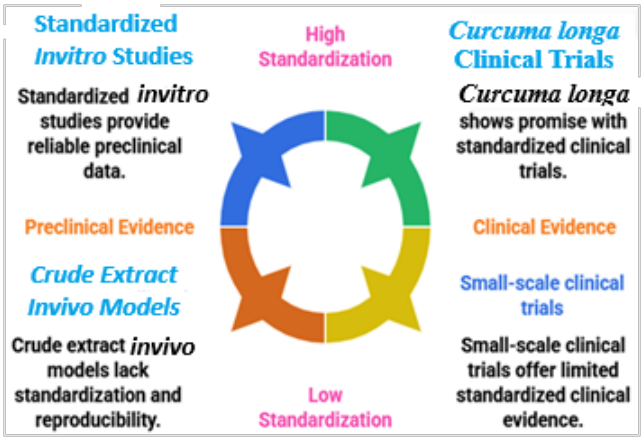


Figure 3. Herbal JAK/STAT modulators research landscape.

6.4 Safety and Standardisation Concerns

Varying composition, purity, and dosing in the different preparations is one of the greatest obstacles to the inclusion of herbal remedies into mainstream treatment. The phytochemical composition of herbal extracts may vary across batches and create a possibility of variation in efficacy and safety. Moreover, the majority of the herbal compounds have not been exhaustively tested on long-term safety, particularly in immunocompromised patients or chronically ill patients[36]. Issues such as herb-drug interactions and hepatotoxicity also warrant caution. Regulatory agencies emphasise the need for standardisation, quality control, and toxicity profiling to ensure safe use. The next phase of clinical studies is to include well-characterised, GMP-qualified herbal formulations of predictable bioactive concentration and proven safety.

7. Integrative and Systems Biology Approach

7.1 Network Pharmacology for Herbal Combinations

The concept of network pharmacology has come to the forefront to find solutions to those complicated interactions of herbal compounds with biological systems, especially multi-component therapy. In contrast to man-made mono-specific drugs, the composition of herbal formulations usually has tens of bioactives against multiple nodes of disease networks. In the context of JAK/STAT modulation, network pharmacology allows the mapping of phytochemicals to their putative protein targets, including JAKs, STATs, upstream cytokines (e.g., IL-6, IFN-γ), and co-regulatory pathways like NF-κB and MAPK[37]. This unified strategy promotes the discovery of synergistic combinations of herbs that affect more than one

signalling axis, thereby providing a systems approach to immune modulation in chronic inflammatory diseases.

7.2 Molecular Docking and ADME Prediction

Technical improvement in the field of computational biology has made it possible to screen the plant-derived compounds against proteins of the JAK/STAT pathways virtually. Docking-based analyses are beneficial in the prediction of binding potential and binding pattern of herbal bioactivities and biological targets JAK1, JAK2 and STAT3. For example, curcumin, withaferin A, and berberine have been shown to bind the ATP-binding pockets of JAKs, suggesting competitive inhibition[38]. Another source of success is through the prediction of ADME (Absorption, Distribution, Metabolism, and Excretion) characteristics of drugs; the use of prediction tools in these areas assists in screening candidates with good oral bioavailability, metabolic stability, and minimal toxicity.

7.3 Role of AI in Screening JAK/STAT Herbal Modulators

The use of Artificial Intelligence (AI) and Machine Learning (ML) is being used more and more frequently to predict and optimise the composition of herbal formulations that have a specific pathway in mind. Artificial intelligence-based systems have the potential to house omics data, libraries of chemical structures, and predications of bioactivity to be used to find new JAK/STAT modulators in large herbal databases[39]. The tools are also useful in clustering structurally related compounds, herb-modelling pharmacophore and optimising synergistic effect in multi-component herbal treatments. Moreover, AI-driven predictions can significantly reduce time and cost in early-phase drug discovery, offering a scalable framework for identifying natural immunomodulators with high precision.

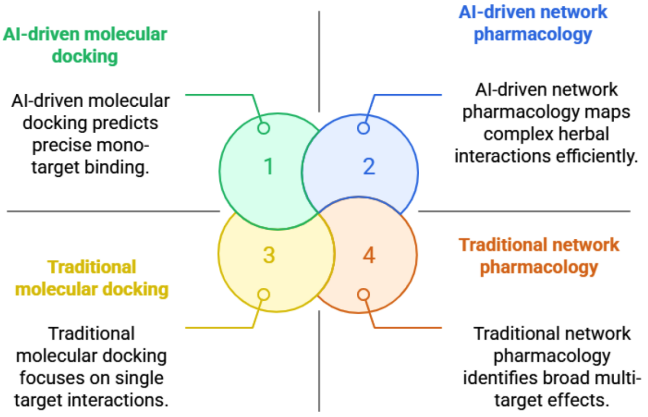


Figure 4. Herbal compound effects and screening methods.

7.4 Multi-target *vs.* Mono-target Effects

The possibility of multi-targeting action is also a major strength of herbal therapeutics, as the aetiology of the chronic inflammatory and autoimmune diseases is multifactorial. Whereas synthetic JAK inhibitors tend to selectively target a single or two JAK isoforms, natural substances such as curcumin or andrographolide exert their effects on several targets together, such as the STATs, cytokines or NF-kB signalling systems, oxidative stress pathways, to name but a few[40]. This polypharmacology can yield broader therapeutic outcomes and reduce the risk of resistance. However, it also complicates mechanistic validation and necessitates more sophisticated models to evaluate efficacy and safety. The systems biology methods, hence, provide a perfect map of fitting into these complex interactions and putting them to use (Figure 4).

8. Challenges and Research Gaps

8.1 Lack of Clinical Standardisation

The lack of common formulations of herbal JAK / STAT modulators is one of the major challenges to the adoption of the process into clinical practice. Going by herbs, they tend to have variable concentration, purity, and bioactivity as they are produced differently, as far as cultivation, harvesting, and extraction are concerned. Such inconsistency interferes with reproducibility, regulatory approval, and it is challenging to compare results among studies[41]. The lack of pharmacopoeial standards and validated markers for quality control remains a significant barrier to the acceptance of herbal immunomodulators in evidence-based medicine.

8.2 Bioavailability Issues

Poor Oral bioavailability is a problem for many herbal compounds with good preclinical effects. Low solubility, high pharmacokinetic rate and poor systemic absorption characterise phytochemicals like curcumin, resveratrol and berberine; features that do not augur well for the therapeutic value of these

molecules *in vivo*. Efforts such as nanoformulations, liposomes, and phytosomes have shown some success in enhancing delivery, but these strategies require further optimisation and clinical validation. Solving the challenge of bioavailability is a necessary step in herbal JAK/STAT modulator transition from the bench to the bedside[42].

8.3 Need for Controlled Clinical Trials

Despite extensive *in vitro* and *in vivo* evidence, few herbal formulations have been rigorously tested in randomised controlled trials (RCTs) for their effects on JAK/STAT-related diseases. Current clinical trials are usually characterised by small subject numbers, unblinded, and a short-period of time. To conclude, there is an urgent need to address the nature of science that will vindicate the safety, efficacy, and dose parameters of herbal immunotherapeutics through large, multi-centric, placebo-controlled trials with well-characterised endpoints and standardised interventions[43].

8.4 Herb-drug Interactions

Another critical concern is the potential for herb-drug interactions, especially in patients with autoimmune diseases who are often on long-term pharmacotherapy. Plants have the potential to interact with drug-metabolising enzymes (e.g., CYP450), change the transporter proteins, or interact with the conventional immunosuppressor to produce adverse effects or lower the effectiveness of a drug. To illustrate, berberine can interact with the cyclosporine metabolism, through the green tea polyphenols, there might be a potential methotrexate interaction. A thorough understanding of these interactions is essential for developing safe integrative treatment regimens[44].

9. Conclusion

The JAK/STAT signalling pathway plays a central role in the pathogenesis of a wide range of chronic inflammatory and autoimmune disorders. Herbal formulas with their wide range of phytochemicals provide promising substitutes to synthetic JAK inhibitors by exerting an anti-inflammatory effect by engaging in this pathway through multiple mechanisms such as direct inhibition of the kinase, dampening cytokine activity and interactions with the other inflammatory pathways[45]. Significant herbs, including *Curcuma longa*, *Withania somnifera*, *Berberis vulgaris*, and *Tripterygium wilfordii,* have proven preclinical effectiveness in maintaining the homeostatic JAK/STAT mechanism in an assortment of diseases, including rheumatoid arthritis, psoriasis, inflammatory bowel disease, and systemic lupus disorder. These botanicals have a potential therapeutic effect besides having a good safety profile, unlike conventional drugs[46]. Nevertheless, to best utilise their clinical potential, standardised formulations, properly designed clinical trials, and integrative approaches of systems biology must emerge with a sense of urgency. The next steps ahead would be the crucial, rigorous translational research that would prove herbal JAK/STAT modulators a useful part of evidence-based and personalised medicine.

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