An Updated Review on Plant Derived Janus Kinase Inhibitors Against Rheumatoid Arthritis

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Abstract:

Rheumatoid arthritis is the most disabling autoimmune condition with persistent inflammation and severe joint destruction. Research conducted in the last decade points to the JAK/STAT signaling pathway as a new contender in the management of RA. The new DMARDs that have been recently approved by the FDA as JAK/STAT pathway inhibitors have come into prominence over the recent years. However, the associated risks of thromboembolism, gastrointestinal side effects, liver damage, and other conditions such as tuberculosis and herpes zoster that come with the use of and administering DMARDs should not be overlooked. Furthermore, they are all considerably pricey, which renders them less suitable for widespread use. These restrictions allow the exploration of new JAK/STAT inhibitors obtained via natural sources which are safer, more cost-efficient, and better tolerated. This review emphasizes the premise of plant-derived JAK inhibitors becoming putative therapeutics of RA. Emodin, mangiferin, apigenin, quercetin, kaempferol etc. exhibit significant JAK inhibitory and anti-inflammatory effects among numerous natural compounds. Plant-derived inhibitors display improved safety profiles and less adverse effects compared to synthetic drugs. Here, we review the mechanisms of action of such natural compounds, their in vitro & in vivo efficacy, as well as the challenges we might face in the development process of RA therapies. Hence, the JAK inhibitors from natural products represent an interesting path forward, showing promise for safe and effective management of patients.

Keywords: Plant Derived Compound, JAK-STAT pathway, Cytokines, Inflammations, Rheumatoid Arthritis.

1. Introduction:

The chronic inflammatory disease known as rheumatoid arthritis that affects 0.5% to 1% around the globe, with increased prevalence in North America and Northern Europe [1]. It is more prevalent in women and develops between 30-50 years. Ethnic and racial inequalities exist, with higher prevalence rates in Native American tribes and lower rates in rural West Africa and Asian countries. Genetic variables, environmental risk factors, smoking, and socioeconomic status also contribute to RA's

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epidemiology. Management is likely long-term, involving complex interplays of contraceptives, genetics, environmental factors, and socio-economic risk variables. Joint distress, edema, and rigidity are prevalent complaints in rheumatoid arthritis (RA), which can contribute to joint malformations and other organ issues. Untreated RA can cause rheumatoid nodules, pulmonary, cardiovascular, ophthalmic, neurological, muscular deficits, osteoporosis, vasculitis, Raynaud's phenomenon, and renal issues. Infrequent problems from extra-articular secondary involvement include firm subcutaneous nodules, lung, eye, heart, kidney involvement, neurological impairments, muscle atrophy, osteoporosis, vasculitis, and Raynaud's phenomenon. Standard drugs like NSAIDs provide symptomatic relief but lack underlying disease modification. Corticosteroids are effective but have adverse effects. Alternatives include conventional DMARDs, biologic DMARDs, and JAK inhibitors. Each has drawbacks like delayed action, high cost, and increased infection risks. Physical therapy and surgical options are limited by location, availability, and pricing. Biologic DMARDs are expensive and effective but limited globally. Customized medicine offers potential for improving outcomes, but long-term use poses risks.

Recent research on rheumatoid arthritis-specific autoantibodies have provided insights into the autoimmune response in arthritis [1]. Understanding the origin of the illness depends critically on these autoantibodies, which target posttranslational modifications. Recent technical breakthroughs allow the procurement of ACPA monoclonal antibodies and the identification and characterization of citrulline-reactive B cells, significantly expanding our knowledge of RA. About one percent of people worldwide suffer with rheumatoid arthritis is largely caused by the hyper activated Janus kinase pathway, which is involved in inflammation, joint destruction, and systemic consequences. Inhibitors targeting the Janus kinase pathway have shown effective in RA [2], although they must be carefully monitored owing to possible hazards.

Herbs have played a crucial role in conventional medicine systems for thousands of years, with evidence of medicinal practices involving plant extracts dating back to ancient civilizations like China, India, and the Middle East. Traditional Chinese Medicine and Ayurveda use plants for inflammation reduction, with examples including Withania somnifera and Boswellia serrata [3]. Plant-derived compounds, such as curcumin, resveratrol, cryptotanshinone, quercetin, and EGCG, have been used historically to treat inflammation [4]. Recent scientific studies have focused on plant-derived JAK inhibitors due to their immuno-modulatory effects and fewer adverse effects compared to synthetic medications. These plant-derived JAK inhibitors have a higher therapeutic value due to their safety, affordability, and efficacy. They are safer, more sustainable, and more holistic than synthetic pharmaceuticals. The search for novel JAK inhibitors from plants is a breakthrough in medicine, opening a vista for patients with inflammation and autoimmune disorders.

2. Overview of JAK-STAT Signaling Pathway:

This pathway, named after a Roman god, is a crucial signaling mechanism that regulates cellular processes, particularly in the immune system. The discovery in [5], 1991 provided insight into how signals are initiated at the cell surface, and how these proteins activate in response to JAKs [6]. Dysregulation of this pathway leads to

metabolic diseases. It facilitates signal transfer from the cell surface to the nuclear level, affecting immune response, mitosis, meiosis, and apoptosis. The JAK-STAT pathway consists of cytokine receptors, janus kinases [7], and signal transducers and activators of transcriptions. JAK proteins are not having dedicated receptor to bind tyrosine kinases, while STATs are proteins that can translocate to the nucleus and transfer signals. JAKs have four family members and seven STATs. JAKs have a FERM domain, SH2-related domain, kinase domain, and pseudokinase domains. STATs also have transcriptional activation domains. Therapeutic interventions focus on JAKs to disrupt wrong signal activation, leading to STAT3 inhibitors. STAT1 and STAT2 have antiviral functions, while STAT3 and STAT5 are involved in immune cell differentiation and activation. Targeting STAT proteins is challenging due to their structure and function.

2.1. Mechanism of JAK/STAT pathway in Rheumatoid Arthritis: The pathway, discovered in 1995, links cell surface receptor activation and gene expression changes. It's linked to immune regulation and development, and its dysregulation is linked to autoimmune disorders, cancers, and inflammatory diseases. Current review explores its role in immune regulation, and potential therapeutic applications in figure 1.

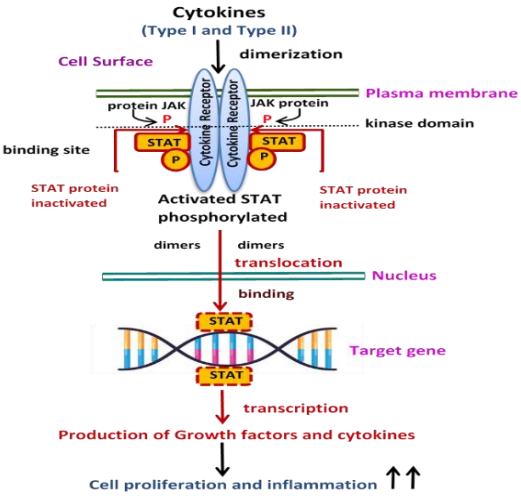

Figure 1: Mechanism of JAK/STAT Pathway [8]

JAKs, a type of protein, are activated through cytokine binding, allowing them to phosphorylate other proteins like STATs. STATs control gene expression and are related to specific biological processes, such as immune response and cell survival. This kinase signaling pathway involves cytokine binding to receptors, causing JAK phosphorylation. Phosphorylated STATs dimerize and translocate to the nucleus, where they modulate gene transcription. To minimize signaling, negative feedback mechanisms like SOCS proteins, Protein Tyrosine Phosphatases and Protein Inhibitors of Activated STAT (PIAS) proteins are used [9, 10]. These mechanisms

ensure well-regulated downstream gene expression, playing a crucial role in immune response, growth, and development. Abnormal regulation may lead to pathological conditions.

2.2. Specific JAK Isoforms Involved in RA by including specific pathways and cytokines involved: A key function for JAK1 in the pathophysiology of RA by regulating the signaling of inflammatory mediators like interleukins, cytokines and IFNs. Abnormalities in IL-6 signaling lead to increased synthesis of pro-inflammatory cytokines, fostering synovitis and joint erosion. JAK2 is associated with hematopoiesis and depends on GM-CSF for macrophage activation and survival. Unusual control of JAK3 signaling increases effector T cells, triggering inflammation and autoimmune reactions.

3. Pathophysiological Consequences by JAK inhibitors in RA:

RA is accompanied with T-cell and B-cell activation that results to inflammation and autoantibody synthesis [11]. JAK inhibitors inhibit cytokines such as IL-6, IL-12 and IL-23, thus inhibiting T and B-cell activation and consequently minimising pathogenic autoantibody formation [12]. Further, these inhibitors prevent activation of synovial fibroblast and reduces the MMP release and cartilage degradation. They also inhibit osteoclast differentiation that minimizes bone resorption and inflammation that has a potential to decrease associate comorbid risks of RA [13]. Thus, due to their unique mechanism of action on the inflammatory processes, JAK inhibitors have disease-modifying impact on the RA structure and patients' characteristics in figure 2.

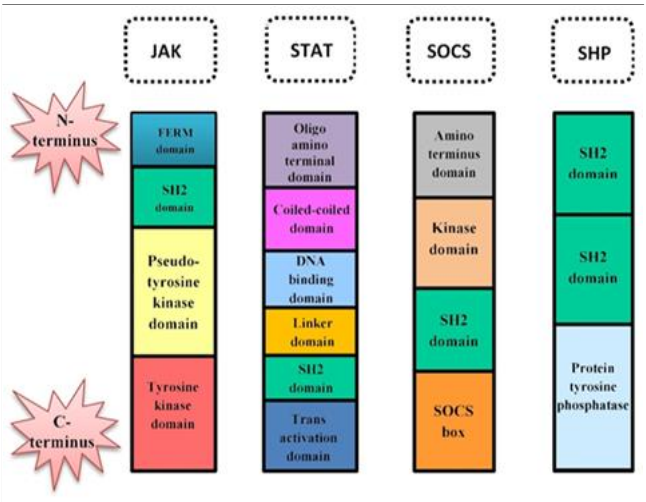

Figure 2: Functional domain associated with JAK and STAT protein [14]

JAKs have a JAK homology domain, crucial for interaction with protein kinases, receptors, enzyme activity, auto-phosphorylation, and inhibiting activity, while STAT proteins are latent cytoplasmic proteins translocated to cytokine/receptor complex. This recruitment leads to the formation of p-STAT dimers, which remains the most efficient way through which STAT proteins are transported into the nucleus and bind

to DNA motifs that has STAT response elements and function as transcription factors [15]. Some known constitutively active signaling is in several types of cancers such as lymphoma, leukaemia, myeloproliferative diseases, solid tumour, and some immunodeficiency syndromes. That there was an increase in a family of proteins that were known to interact with STATs and inhibit their activity, the suppressor of cytokine signaling (SOCS) proteins, showed that the presence of SOCS was thus likely to be the direct mechanism by which the JAK/STAT signaling pathway was negatively regulated. In RA, negative regulation of Stat protein activation via SOCS was also identified as being extraordinarily compromised [16–19].

For that reason, the pathophysiological consequences of blocking JAK in RA are not confined to the relief of mere symptoms. Through the inhibition of the JAK proteins, which are involved in cytokine signalling, JAK inhibitors alter immune response, decrease synovitis and halt articular cartilage development. JAK inhibitors are useful treatment alternatives for people who do not react to normal medication, but they may erode internal organs and raise the possibility of consequences. However, they should be monitored for adverse effects to enhance their therapeutic gains in patients to reduce risk factors.

4. Clinical Implications by JAK Inhibitors in RA:

JAK or STAT gene mutations can lead to immuno-deficiencies, drawing attention to the significance of the JAK-STAT pathway in immune responses. For effective management of a wide variety of diseases, it is imperative that therapeutic approaches target the JAK-STAT signaling cascade, where JAK inhibitors remain crucial components of treatment strategies. JAK inhibitors such as Tofacitinib and Baricitinib thereby applied inhibit this process, thereby lowering inflammation and immune system response.

From table 1 JAK inhibitors, such as tofacitinib and ruxolitinib, are used to treat rheumatoid arthritis and myelofibrosis. Consequently, Janus kinase signaling appears as an attractive area for drug development against several diseases and small molecules disrupt JAK activity reducing inflammation and abnormal proliferation of cells.

Table 1: Overview on some Synthetic JAKinibs

Synthetic JAKinibs	Specificity	FDA approved	Adverse effects
Upadacitinib	JAK1	Yes; Brand Name-RINVOQ® (RINVOQ, 2019)	Severe infections, malignancies, elevated lipid parameters, low blood cell counts, stroke, venous thrombo-embolism [20].
Tofacitinib	JAK1, JAK3	Yes; XELJANZ® (Padda et al., 2023) (U.S.	Severe infections, gastrointerstinal perforation, thromboembolism [21].

		FDA Approves Pfizer's XELJANZ® (Tofacitinib) For The Treatment of Active Ankylosing Spondylitis | Pfizer, n.d.)	
Filgotinib	JAK1	-	Nasopharyngitis, headache, infections [22–24].
Baricitinib	JAK1, JAK2	Yes; OLUMIANT® (Eli Lilly and Company, 2022)	Infections, hyperlipidaemia [25].
Decernotinib	JAK3	-	Neutropenia, lymphopenia, hyperlipidaemia, elevated hepatic transaminases [26].
Peficitinib	JAK3	-	Severe infections, gastrointestinal perforation, sepsis, plasma CK increase, lymphopenia [27].

These drugs through the above mentioned ways of reducing cytokine signaling, the activity of certain JAK proteins limits inflammatory gene transcription. This results in the overall reduced recruitment of immune cells into the synovium of RA patients, inflammation thereby treating the symptoms of joint pain and swelling. JAK inhibitors have proved efficiency in the regulation and interruption of the inflammatory process that leads to joint erosions in RA patients which makes them a rational point of therapeutic intervention. Another JAK inhibitor known as Upadacitinib selectively inhibits various cytokines in inflammation catering for overall treatment. JAK inhibition appears to hold great potential for reducing RA symptoms because it acts to regulate pro-inflammatory cytokine signaling and immune response [28].

5. Plant Derived Compounds with JAK Inhibitory activity:

From table 2 the Janus kinase (JAK) signaling pathway is crucial in rheumatoid arthritis, with synthetic inhibitors being effective, but plant-derived substances with JAK inhibitory action offer potential therapeutic benefits in figure 3.

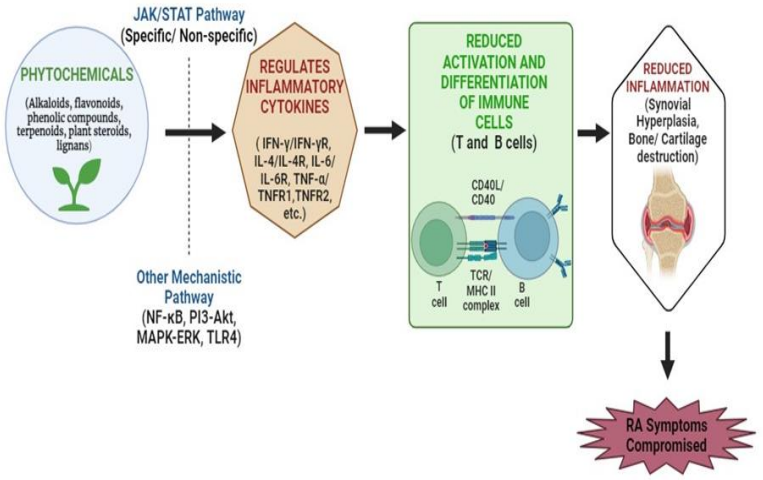

Figure 3: Phytochemicals targeting RA by JAK/STAT inhibition [29]

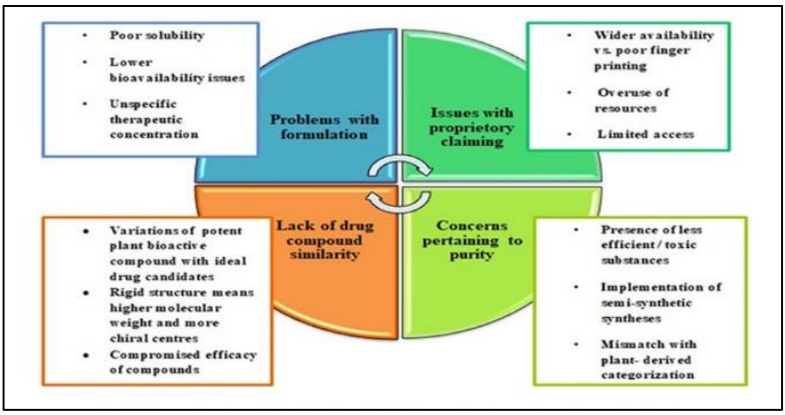

Figure 4: Benefits and limitations with plant derived compounds

Emodin, a compound found in plants like Rheum palmatum, Reynoutria japonica, Polygonum multiflorum, Rhamnus cathartica, Frangula alnus, and Aloe vera, has been found to possess anti-inflammatory, immunosuppressive, and antioxidant properties, potentially aiding in the management of RA by suppressing pro-inflammatory cytokines, reducing synovial proliferation, inhibiting osteoclast differentiation, and moderating immunologic responses. The recent endeavours regarding the studies conducted on animal specimens suggest that Emodin does reverse Joint Swelling or Oedema, Cartilage Degeneration, and bone erosion in the CIA and AIA animal models [30]. One or two papers also show that soluble emodin might enhance the efficiency of one or more of the first-line RA treatments, including methotrexate, which can possibly lessen the signs of inflammation, but likely also reduce the adverse effects of the medicines concurrently [31]. Emodin is determined

to possess low level of toxicity in majority of the experiments but reported to have gastro intestinal side effects whenever administered in higher concentrations because of its natural laxative property in figure 4.

Quercetin is scientifically classified as a flavonoid which can be identified in a variety of fruits and vegetables as well as in medicinal plants. They are known to exhibit actions such as; anti-inflammatory, antioxidant activity alongside immunomodulation. In vitro quercetin exhibits both inflammatory and autoimmune effect which possibly can used after rational manner to rheumatoid arthritis therapy [32]. Worthing capability described in preclinical studies concerns the following; regulation of the level of pro-inflammatory cytokines, inhibition of NF-κB and MAPK signaling cascade, reduction of the level of oxidative stress, prohibitory effect upon synovium hypertrophy and cartilage degradation, inhibition of osteoclast formation and their activity. Moreover, quercetin influences the activity of immune cells and can thus aid in controlling autoimmune processes responsible for RA.

Kaempferol is obtained from several fruits, vegetables, and medicinal plants indicates it has anti-inflammatory, antioxidant characteristics, and immuno-modulatory potential [33]. It is a bioactive compound which has shown anti-inflammatory properties in joint tissues, suppressing inflammatory cytokines and inhibiting NF-κB and MAPKs translocation. It also controls immune cell functions, particularly in rheumatoid arthritis, by modulating immune cell enhancement. Kaempferol reduces ROS levels in joint tissues, preventing oxidative and inflammation injury. Its potential for therapeutic targeting in rheumatoid arthritis is significant due to its inflammatory, antioxidant, and immunomodulating effects [34].

Luteolin, a flavonoid found in plants, fruits, and vegetables, has potential as a treatment for rheumatoid arthritis (RA). It has bioactive anti-inflammatory, antioxidant, and immunomodulatory properties, targeting cytokine production, NF-κB, JAK/STAT pathway MMPs, and cellular oxidation. Luteolin has shown effectiveness in experimental models and has no toxicity at therapeutic doses. However, its therapeutic efficacy in humans remains to be tested [35, 36].

Mangiferin, a xanthonoid from mango and medicinal plants, has anti-inflammatory, antioxidant, and immunomodulatory effects. Studies show it modulates pro-inflammatory cytokines, reduces joint inflammation, and reduces cartilage loss and bone erosion. In animal models, it reduces inflammation and improves arthritic manifestations [37]. However, toxicity studies show negligible adverse effects at therapeutic levels. Further clinical trials are needed to confirm these results from human subjects. Pharmacokinetic and toxicity studies are needed to confirm these findings.

Sinomenine, an alkaloid from Sinomenium acutum, has shown potential therapeutic efficacy in rheumatoid arthritis (RA). It targets the janus kinase signaling pathway, which controls immune and inflammatory signaling. By blocking JAK1/2 and STAT3 proteins, Sinomenine downregulates pro-inflammatory molecules and inhibits the release of other mediators of inflammation. In the collagen-induced arthritis (CIA) animal model, sinomenine suppresses synovial thickening and infiltration of inflammatory cells, and alleviates bone resorption in the murine model. In the adjuvant-induced arthritis mouse model, sinomenine reduces joint swelling,

inflammation, and bone erosion. While sinomenine has no significant toxic effects at therapeutic concentrations, high concentrations may increase toxicity [38].

Oxymatrine, derived from Sophora flavescens root, has potential as a drug candidate for autoimmune diorders, particularly rheumatoid arthritis. It can suppress kinase cell signaling pathways, which are involved in leukocyte differentiation and cytokine synthesis. Oxymatrine has been shown to inhibit these pathways, reduce pro-inflammatory cytokines, regulate immune cell activation, inhibit fibroblast proliferation, and protect joint tissue. However, more long-term safety data is needed to estimate associated risks. Further clinical studies are needed to evaluate the effectiveness and toxicity of oxymatrine for human RA patients with side effects [39].

Piper longum, an ethnopharmacological plant used in Ayurveda, has been found to be an effective modulator of this pathway. Piper longum extracts, particularly a piperine component, have been shown to minimize inflammation and immune reactions in RA. Piper longum also has antioxidant properties that decrease oxidative stress, which contribute to joint degeneration. Studies using CIA and AIA rat models have shown initial effectiveness in reducing cytokines released into the inflammatory microenvironment. Combining Piper longum with conventional treatments like methotrexate and JAK inhibitors may be effective due to the piperine effect.

Chamomile, celery, and parsley contain flavonoid apigenin, which may have anti-inflammatory properties and potentially compete with JAK/STAT in RA treatment. Such cytokines that sustains inflammation in RA include the interleukin 6 (IL-6), interferon- γ (IFN-γ) and the granulocyte-macrophage colony stimulating factor signaling through the JAK/STAT pathways [40]. Apigenin, a JAK inhibitor, has therapeutic properties by downregulating the JAK/STAT signal transduction pathway, reducing pro-inflammatory cytokines, suppressing synovial cell proliferation, modulating immunological cell activity, and inhibiting osteoclast formation. It reduces joint inflammation, cartilage degradation, and bone loss in experimental models. Apigenin's safety profile is safer than many other drugs, making it a recommended anti-RA medication.

Rosmarinic acid, a polyphenolic derivative found in medicinal plants like Rosmarinus officinalis, Salvia officinalis, and Melissa officinalis, has shown anti-inflammatory, antioxidant, and immunomodulatory activities in animal studies. It controls the JAK-STAT system, inhibits immune cell activation, and regulates osteoclast formation. It has shown anti-arthritic activity in rats, reducing joint stiffness, cartilage breakdown, and bone loss. However, no human studies have been conducted to determine its efficacy and associated risks [41].

Table 2: Phytochemicals targeting RA

Isolated Products	Mechanism	Preclinical Studies
Emodin	Inhibiting IFNAR1 degradation, kinase CK2 and binds to JAK1,JAK2	In Freund's adjuvant-induced arthritis model, arthritic scores and paw volume decreases significantly ($P < 0.001$) [42].

Quercetin	Directly binds to the JAK1/2,STAT3 prevents its activation	Oral dose to chronic rat AIA models results lower levels of MCP-1 ($p < 0.05$) and IL-1β ($p < 0.001$), lipoxygenase in lungs ($p < 0.001$) and liver ($p < 0.001$) [43].
Kaempferol	Reducing JAK protein phosphorylation and STAT transcription factor downstream activation [34].	Effective in CIA model with 20mg/kg intraperitoneal dosage [44].
Luteolin	Reducing the expression of phosphorylated JAK2 and STAT3 proteins	Reduced rat chondrocyte inflammation in vivo and in vitro rat model by blocking IL-1β [35].
Mangiferin	Inhibiting the activation JAK1/2 & STAT1/3 [37].	Induced pyroptosis in in vitro cellular models RAW264.7 and MH7A cells [37].
Sinomenine	Inhibiting JAK2 & STAT 3	Stimulated the reprogramming of macrophages toward an M2-like phenotype via the STAT1. In vivo TNF-α inhibitory activity [38].
Oxymatrine	Inhibiting JAK2 & STAT 3	Balanced Th1/Th2, Treg/Th17, Tfr/Tfh cells in collagen induced rat [39]. Regulated TLR9/MyD88/STAT3 in collagen-induced arthritic mice [39].
Piperlongumine	Inhibiting JAK2 & STAT 3	Decreased nociceptive and arthritic symptoms in rats. Protective against adjuvant-induced arthritis in rats [45].
Apigenin	Blocking the phosphorylation of JAK1/2 & STAT 1/3	Reduced p65, TTR, and RAGE levels. Decreased production of pro-inflammatory cytokines [46].
Rosmarinic acid	Suppress JAK1/2/3	Rduced MPO and NO levels in

	& STAT1/3[47].	in vivo study. Effective in in vitro study with a dose of 10 mg/kg [47].

6. Conclusion:

In the past decade, the therapy for rheumatoid arthritis has experienced a quite of a transition due to the introduction of biologics that addresses inflammatory chemicals. Some of the JAKinibs which are JAK inhibitors and could be orally administered has been found to be as effective as biologics in the treatment of rheumatoid arthritis RA. At the current stage of development of the pharmacology of RA treatment is available in a large number of synthetic drugs. However, the unwanted effects of these medicines are not concealed from us; therefore, there is a creation of herbal drugs to treat RA. Synthetic drugs can cause various side effects like gastrointestinal perforation, thromboembolism, hyperlipidemia, anemia, neutropenia, hypokalemia, infections, malignancies, elevated lipid parameters, low blood cell counts, stroke, and venous thromboembolisms. Possible side effects of synthetic pharmaceutical products might be averted through reducing using in the RA treatment since the similar efficiency might be achieved with the help of the herbal medicine more without variety of negative side effects. There are also cheap options but further studies needed for better clinical, preclinical safety assessments, dosage stability and sustainability. Innovations found in the herbal products such as phytopharmaceuticals, nutraceuticals in the near future tends to contribute significantly to RA therapy.

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