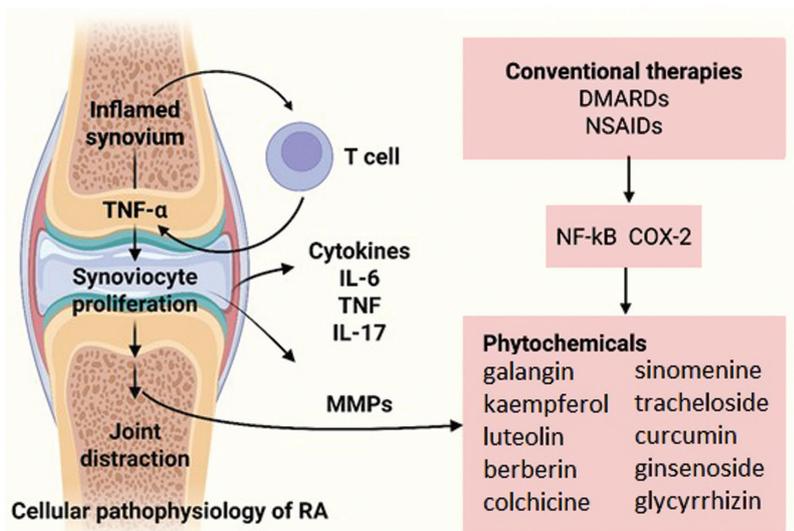


Phytochemicals as a Promising Approach to Rheumatoid Arthritis: Current Perspectives

Graphical abstract



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In brief

Graphical representation of cellular pathophysiology of rheumatoid arthritis, highlighting therapeutic intervention points for both conventional therapy and medicinal plant-derived phytochemicals (figure created with BioRender.com).

Highlights

- Phytochemicals such as flavonoids, alkaloids, and terpenoids target key inflammatory pathways (NF-κB, MAPK, and JAK/STAT) and cytokines (TNF-α and IL-6) to exert anti-inflammatory effects in rheumatoid arthritis models.
- These compounds have synergistic and multi-targeting properties in that they act on both inflammatory and oxidative stress pathways.
- Lack of standardization, poor bioavailability, and insufficient clinical information are some of the key issues involved in clinical translation.
- Promising strategies to expand efficacy involve nanoformulations, combination therapies with DMARDs, and well-designed clinical trials with standardized preparations and pharmacokinetic valuations.

Phytochemicals as a Promising Approach to Rheumatoid Arthritis: Current Perspectives

Vidhan Chand Bala^{1,*} and Asheesh Kumar Gupta¹

Abstract

In recent years, phytochemicals and medicinal plants have increasingly been used to treat autoimmune diseases, such as rheumatoid arthritis (RA). RA, a systemic inflammatory disease, is a chronic condition that affects primarily the joints, which are lined by synovial membranes, and leads to pain, diminished mobility, and joint deterioration. Oxidative stress, synovial hyperplasia, immune cell infiltration, and the production of pro-inflammatory cytokines, such as TNF- α and IL-6, are key factors in RA development. Herbal medicine is an effective alternative to conventional treatments, such as biologics, nonsteroidal anti-inflammatory drugs, and disease-modifying antirheumatic drugs, which are commonly used but can lose effectiveness or cause adverse effects. Phytotherapy therefore provides a promising complementary approach. This review provides an in-depth analysis of the pathophysiology of RA, therapeutic targets, drug resistance, and current therapeutic boundaries, with a focus on the roles of phytochemicals such as lignans, flavonoids, alkaloids, terpenoids, and phenolic compounds. By targeting key pro-inflammatory cytokines such as TNF- α and IL-6, and reformed molecular pathways such as those involving NF- κ B, MAPK, and Nrf2/HO-1, these phytochemicals have potent anti-inflammatory and anti-rheumatoid arthritis properties.

Keywords

Anti-inflammatory; autoimmune disease; medicinal plants; phytochemicals; rheumatoid arthritis.

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Introduction

Rheumatoid arthritis (RA) is a condition that causes joint inflammation, and leads to bone and cartilage damage. Approximately 0.5–1% of people worldwide are affected, particularly women between 40 and 60 years of age [1, 2]. Reactive oxygen species (ROS), matrix metalloproteinases (MMPs), pro-inflammatory cytokines (including tumor necrosis factor (TNF)- α , interleukin [IL]-1 β , IL-6, and IL-17), and other mediators are overproduced as a result of immune dysregulation, which prolongs joint injury [3, 4]. Current treatments, including disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, biologics, corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs), can halt disease progression but frequently have substantial adverse effects (hepatotoxicity and infection risk) and poor long-term efficacy [5, 6]. Many patients turn to alternative therapies because traditional medications cannot completely regulate cytokine cascades or oxidative stress [7, 8].

Natural chemicals originating from plants have garnered increasing attention as potential new treatments for RA. Alkaloids, flavonoids, terpenoids, phenolic compounds, saponins, tannins, lignans, and other chemical groups are among the many bioactive phytochemicals found in medicinal plants, which have long been used to treat inflammatory diseases [9–12]. In preclinical settings, many of these substances show strong antioxidant and anti-inflammatory properties. For example, triterpenoid saponins inhibit the nuclear factor-kappa B (NF- κ B) pathway and consequently decrease inflammatory responses, whereas flavonoids target IL-6 and TNF- α , key cytokines involved in RA pathogenesis. Numerous exemplary phytochemicals have been examined in autoimmune disease studies [13]. Interestingly, phytochemicals frequently work by controlling molecular pathways that jointly decrease pro-inflammatory mediators and increase anti-inflammatory cytokines [14].

Cytokine production, NF- κ B/mitogen-activated protein kinase (MAPK)

signaling, oxidative stress, and inflammatory enzymes are generally targets of RA management [15]. Whereas phytochemicals may exert their effects on overlapping pathways with possibly fewer negative effects, conventional DMARDs target immunosuppression. For example, many phytochemicals suppress downstream cytokine release through the obstructive NLRP3 inflammasome pathway, cyclooxygenase-2 (COX-2) expression, or NF- κ B activation [16, 17]. Additionally, they support antioxidant defenses by upregulating enzymes including superoxide dismutase (SOD) in the response to ROS by inflammatory synovium [18–20].

Preclinical research evaluating phytochemicals in RA models has markedly increased in the past decade. This research has involved both *in vivo* animal models (such as collagen-induced arthritis [CIA] and adjuvant-induced arthritis [AIA]) and *in vitro* experiments (such as lipopolysaccharide [LPS]-stimulated synoviocytes). To highlight mechanistic understanding, this review focuses exclusively on preclinical evidence. We explore the sources and effects of phytochemicals by categorizing them into classes, such as flavonoids, alkaloids, terpenoids, phenolic compounds, saponins, tannins, and lignans. Molecular markers such as NF- κ B, MAPK, COX-2, cytokines, and oxidative stress pathways are highlighted. The figures depict key signaling pathways influenced by phytochemicals, whereas the tables summarize plant sources and experimental methods. In the Methods, we define the literature search approach. The potential of phytochemicals as therapeutic mediators for inflammatory illnesses is discussed in the Conclusion, including suggestions for future lines of investigation. This systematic review explains the routes through which phytochemicals decrease inflammation, according to preclinical research. In summary, the study illuminates the ability of phytochemicals to address inflammation and oxidative stress in the framework of RA. Future research should focus on well-designed clinical trials to further explore their therapeutic potential in managing inflammatory diseases.

Literature search

This narrative review was based on a comprehensive literature search conducted in the PubMed, Scopus, and Google Scholar databases, to identify preclinical studies exploring the anti-rheumatoid arthritis potential of phytochemicals and plant-derived compounds. Search terms included rheumatoid arthritis; phytochemicals; plant extract; anti-inflammatory; *in vitro*; *in vivo*; and specific phytochemical classes, such as flavonoids, alkaloids, terpenoids, phenolic compounds, saponins, tannins, and lignans. Both *in vitro* models (e.g., fibroblast-like synoviocytes [FLSs] and RAW 264.7 macrophages) and *in vivo* models (e.g., CIA and AIA) were included when they provided meaningful mechanistic or pharmacological evidence. Clinical and computational studies were excluded except when they contributed helpful perspectives. The collected data included phytochemical identity, plant source, experimental model, molecular targets, and biological effects, such as cytokine modulation, oxidative stress, and histopathological improvements. Overall,

this narrative review provides an overview of preclinical evidence highlighting mechanistic patterns, without indicating systemic evaluation or quantifiable comparison.

Pathophysiology of RA, molecular targets for RA treatment, and the most common pathway

Pathophysiology of RA

RA progression can generally be divided into three interconnected stages: (1) the initiation or preclinical stage, characterized by the initiation of autoreactive T and B cells, and the generation of autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs); (2) the acute or non-specific inflammatory stage, involving synovial inflammation, immune cell infiltration, and cytokine overproduction (e.g., TNF- α , IL-1 β , and IL-6); and (3) the chronic destructive or inflammatory stage, including persistent synovitis indications such as pannus formation, cartilage degradation, and bone erosion [21, 22]. These successive overlapping phases characterize the transition from autoimmune initiation to irreversible joint damage [23].

Initiation or preclinical stage

Autoantibody production is associated with serious symptoms, such as joint damage and elevated risk of death [24], probably because of the production of anti-citrullinated protein antibodies (ACPAs), which form immune complexes with citrullinated antigens. After these complexes bind RFs, complement is activated [25–28]. The ability to identify autoimmune reactions to citrullinated self-proteins has been a major development in recent years. The extent and strength of the association between shared epitopes and ACPA-positive and ACPA-negative epitopes varies among patients with RA. Because several non-HLA genes associated with RA susceptibility show substantial similarity across different genomes, researchers have speculated that ACPA-positive and ACPA-negative RA might be two genetically different forms of RA [29, 30]. Arginine has been shown to be converted into citrulline by peptidylarginine deiminases (PADs) when specific environmental factors change. Citrullinated proteins, after being presented to T cells by antigen-presenting cells via specific major histocompatibility complexes (MHCs), also produce ACPAs and trigger autoimmune reactions to citrullinated self-antigens in patients with RA [32]. Another non-MHC genetic risk factor for RA is peptidyl arginine deiminase type 4 (PADI4). However, in Asian patients with RA, bone injury has been associated with the PADI4 risk allele regardless of ACPA positivity [33]. Activated immune responses in tissues are unknown; however, ACPAs bind citrullinated residues on several proteins, such as histones, vimentin, fibronectin, fibrinogen, type II collagen, and alphaenolase [34]. Pre-RA, or circulating ACPAs, have been identified as many as 10

years before diagnosis [35]. Serum cytokine concentrations rise in tandem with the diversity and concentration of ACPA epitopes over time. ACPA and RF concentrations fall with good treatment, although patients scarcely ever become ACPA negative. In contrast, patients may seroconvert to RF negativity as a result of more frequent and dramatic RF decreases [35]. Autoantibodies directed against other post-translational protein modifications may also form, but anti-carbamylated protein and acetylated protein autoantibodies have also been found in patients with RA [36].

Acute or non-specific inflammatory stage

In RA, synovial inflammation elicited by immunological activation results in joint swelling. Leukocytes entering the synovial compartment are a characteristic of the observed edema [29]. The cellular makeup of RA synovitis is characterized by buildup of innate immune cells (such as dendritic cells, monocytes, mast cells, and innate lymphoid cells) and adaptive immune cells (such as T-helper (Th)1 and Th17 cells, B cells, plasmablasts, and plasma cells). Dendritic cells are stimulated by specific environmental or genetic variables and subsequently stimulate innate immunity [37]. After their recruitment and activation, dendritic cells cause T cells to release proinflammatory and bone-destroying cytokines, such as IL-1 β , IL-6, and TNF- α , as well as MMPs, and to activate B cells, macrophages, synoviocytes, chondrocytes,

and osteoclasts [38]. Therefore, the combination of innate and adaptive immune pathways facilitates tissue damage and remodeling in the nearby bone marrow and synovium [39]. Angiogenesis, which is necessary to provide nutrition and oxygen to enlarged joints, can lead to ongoing inflammation in RA and attract white blood cells to inflamed joints. Angiogenesis is triggered by proangiogenic factors [40]. In the synovium intima, FLSs develop a distinct invasive phenotype that encourages extracellular matrix invasion and aggravates joint damage [41] (Figure 1).

Increasing evidence highlights the critical role of the gut-joint axis in rheumatoid arthritis pathogenesis. Dysbiosis, characterized by diminished microbial diversity and enrichment in pro-inflammatory taxa such as *Prevotella copri*, has been associated with autoimmune activation and loss of immune tolerance. The gut microbiota influences systemic inflammation through modulation of intestinal permeability, LPS translocation, and cytokine production [42]. Many bioactive phytochemicals (such as polyphenols, flavonoids, and alkaloids) exert a portion of their anti-inflammatory effects via the gut microbiota, by enhancing beneficial genera (e.g., *Lactobacillus* and *Bifidobacterium*) and increasing the production of short-chain fatty acids, such as butyrate and propionate. These microbial metabolites regulate regulatory T (Treg) cell differentiation and inhibit Th17-driven cytokine cascades (IL-6, IL-17, and TNF- α), thereby restoring immune homeostasis. This gut microbial metabolism of phytochemicals provides a crucial mechanistic link between

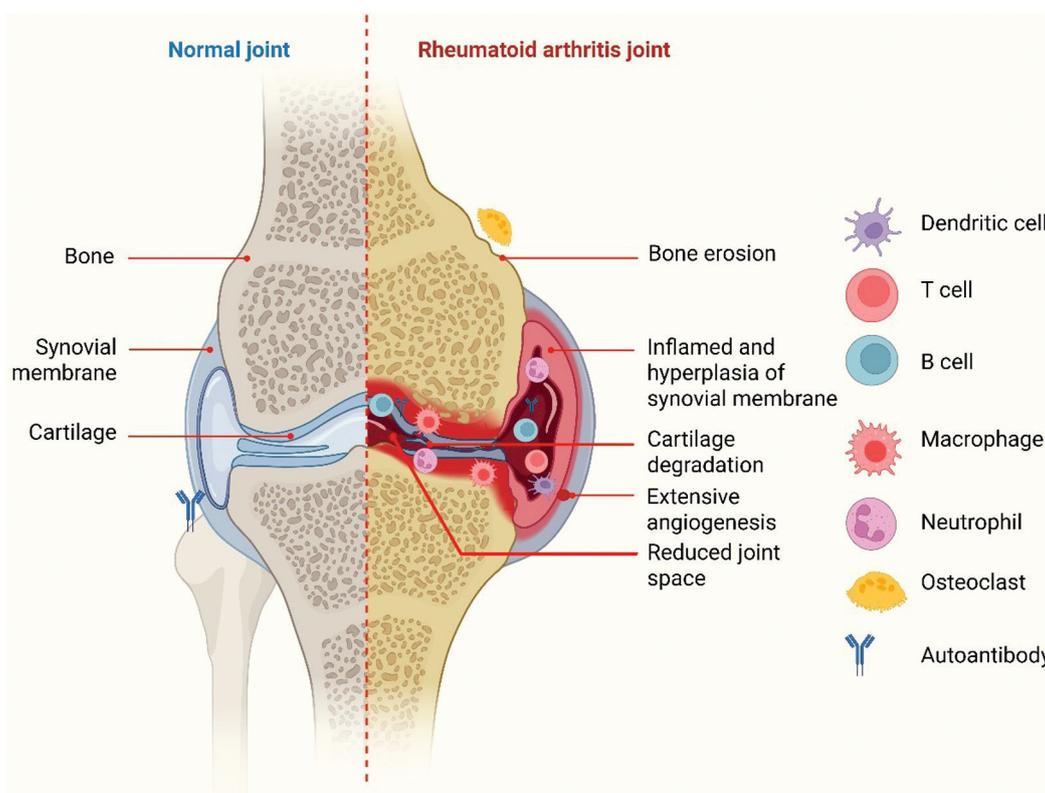


Figure 1 Normal joints and joints with rheumatoid arthritis. In RA, joint swelling reflects immune-stimulated synovial inflammation. T cells, dendritic cells, B cells, macrophages, and osteoclasts are examples of the innate and adaptive immune cells that accumulate in RA sinusitis. Angiogenesis, muscle atrophy, and synovial thickening are caused by immune response components that are pro-inflammatory and bone-destructive, thus resulting in loss of bone or cartilage (figure created with BioRender.com).

dietary or plant-derived compounds and their systemic anti-arthritic effects, and emphasizes the therapeutic relevance of targeting gut dysbiosis alongside joint inflammation in RA [43].

Chronic destructive or inflammatory stage

The nature of immune cells in the development and progression of RA has been examined in recent research. Local interstitial cells and their role in RA pathophysiology have also received increasing attention in recent years. The structural foundation of organs and tissues is made up of stromal cells [44]. These cells are believed to identify infections, initiate immunological responses, and perform immune tasks. Typical stromal cells include fibroblasts found in the gut, skin, gums, and synovium. Innate immune receptors, particularly Toll-like receptors (TLRs), are expressed by these cells [45, 46]. These stromal cells additionally release cytokines and chemokines, and use MHC II receptors to present and express antigens. Consequently, the innate immune system includes these stromal cells [34].

FLSs' typical physiological activity in non-pathological synovial tissue includes forming the synovium's lining layer, secreting synovial fluid, lubricating joint proteins, and supplying plasma protein for the surrounding cartilage and joint cavity [47]. Additionally, by generating matrix components such as collagen, FLSs contribute to the ongoing remodeling of the synovium and preserve synovium homeostasis. FLSs markedly change from benign mesenchymal cells to

aggressive and destructive tumor-like cells when RA inflammation is present [48]. Decreased susceptibility to apoptosis; overexpression of adhesion molecules; and aberrant production of cytokines, chemokines, and MMPs are among the unique characteristics of these altered RA FLSs, which are important in RA development and progression [48].

The inflammatory environment of the synovial compartment is controlled by a complex network of cytokines and chemokines; several clinical interventions have indicated that granulocyte-monocyte colony-stimulating factor, IL-6, and TNF- α are crucial to the process shown in **Figure 2** [49]. By stimulating endothelial cells, drawing immune cells to the synovial compartment, stimulating fibroblasts, and accumulation of activated T and B cells, cytokines and chemokines increase inflammation. Th cells differentiate into Th1, Th2, Th17, and Treg cells, according to the cytokine microenvironment, whereas activated B cells, with the aid of antigen-presenting cells and Th cells, differentiate into plasma cells, which produce and secrete various immunoglobulins. Th1 cytokine secretion increases Th17 infiltration and IL-17 synthesis in synovial tissues during RA [50]. A subpopulation of CD4+ T cells called follicular helper T (Tfh) cells facilitate germinal center responses by supplying the signals required for the development of long-lived antigen-secreting plasma cells and high-affinity antibody synthesis [51]. Uncontrolled proliferation of Tfh cells has been noted in several systemic autoimmune diseases; moreover, in patients with RA, the frequency of circulating Tfh-like cells, their subtypes, and synovially infiltrating Th cells correlate with the disease process [52]. Monocytes and macrophages

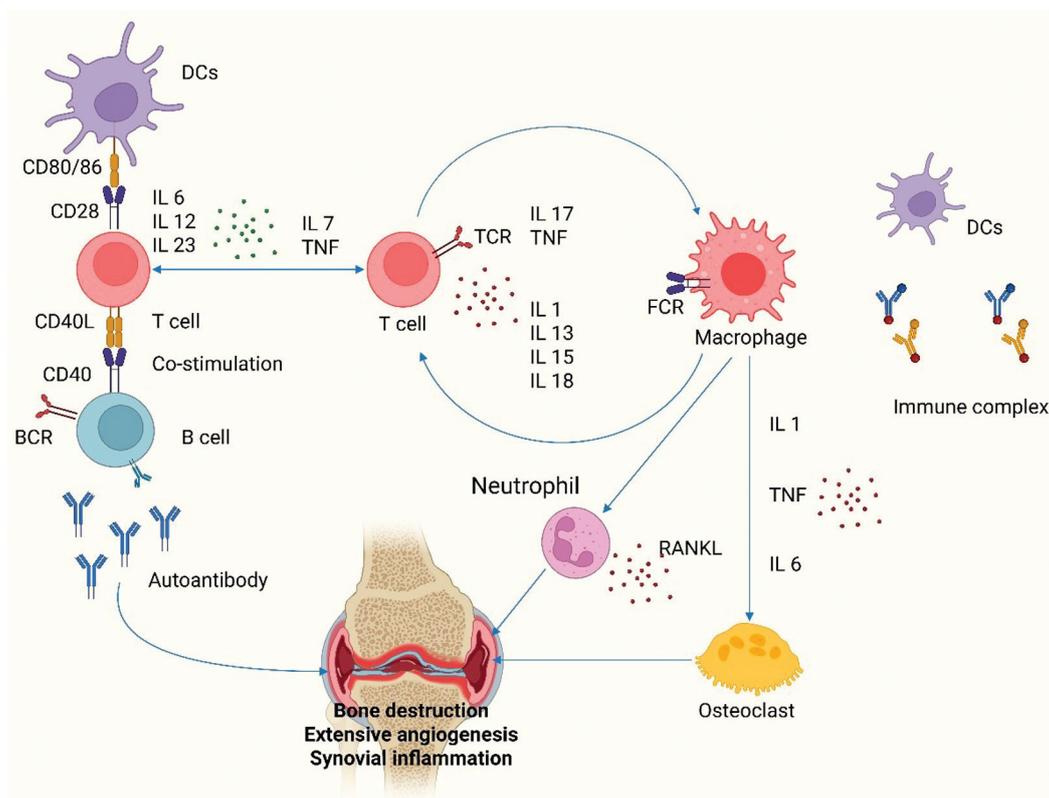


Figure 2 Cellular and cytokine interactions in the pathogenesis of rheumatoid arthritis (figure created with BioRender.com).

use receptor activator of nuclear factor κ B ligand (RANKL) to trigger the generation of osteoclasts, whereas fibroblasts interact directly with the RANK receptor on dendritic cells, macrophages, and preosteoclasts [53]. At the so-called “bare area,” where the periosteal synovial membrane, bone, and cartilage meet, bony erosions occur [54]. Cytokines activate genes encoding systems that can worsen inflammation and cellular and tissue damage by binding homologous receptors and initiating a variety of intracellular signal transduction events [55].

Molecular targets for RA treatment and the most common pathway

Numerous molecular targets and signaling pathways are involved in the intricate pathophysiology of RA, which have been extensively investigated to create efficacious treatment plans. Pro-inflammatory cytokines, immune cells, and intracellular signaling molecules are important molecular targets for RA treatment [56].

TNF- α , a pro-inflammatory cytokine essential to the pathophysiology of RA, is among the best-known molecular targets in RA treatment. Infliximab, adalimumab, and etanercept are examples of TNF- α inhibitors that have demonstrated notable effectiveness in lowering inflammation and delaying the course of disease [57]. IL-1 and IL-6 are other notable cytokine targets. Tocilizumab and other IL-6 receptor inhibitors have shown promise in treating RA symptoms and avoiding joint degeneration [58]. Despite being less frequently used than TNF- α and IL-6 inhibitors, IL-1 receptor antagonists, including anakinra, have demonstrated potential in RA treatment [59].

Immune cell-specific molecules have become notable therapeutic targets in RA, in addition to cytokine targets. Drugs such as rituximab, a monoclonal antibody that depletes CD20-positive B cells, can be used to target B cells, which are essential for autoantibody generation and T cell activation [60]. T cell-targeted treatments, such as abatacept, which binds CD80/CD86 on antigen-presenting cells and subsequently suppresses T cell co-stimulation, have been shown to be effective in RA [61]. A new method of treating RA uses Janus kinase (JAK) inhibitors, such as tofacitinib and baricitinib, which target intracellular signaling pathways implicated in cytokine generation and immune cell activation [44].

The inflammatory cascade involving TNF- α and its downstream signaling molecules is the most frequently identified route associated with the pathophysiology of RA and targeted for therapy [29]. The NF- κ B route, the MAPK system, and the JAK-STAT pathway are among the intracellular signaling pathways activated by TNF- α . Pro-inflammatory mediators, MMPs, and other substances that cause synovial inflammation and joint degradation are produced through these pathways [62]. When the TNF- α pathway interacts with other cytokines, such as IL-6 and IL-1, it forms a network of inflammatory signals. TNF- α inhibitors, which target the TNF- α pathway, are highly successful in controlling RA symptoms and delaying the course of the illness in many individuals [63].

The JAK-STAT signaling system, which is involved in the transmission of signals from many cytokines, such as IL-6, interferon-gamma, and several interleukins, is another important mechanism in RA pathophysiology [64]. JAK inhibitors targeting this route have demonstrated encouraging outcomes in RA treatment, particularly in patients who do not respond well to biologic therapies or traditional DMARDs. The JAK-STAT pathway is a favorable target for RA therapy because it is essential for immune cell activation, differentiation, and cytokine generation [64].

Because B cells aid in the generation of autoantibodies and the activation of T cells, the B cell receptor signaling pathway plays a crucial role in the pathophysiology of RA [65]. Rituximab and other B-cell depletion treatments targeting this pathway have demonstrated effectiveness in controlling RA symptoms and averting joint deterioration. Additionally, as demonstrated by abatacept’s ability to effectively suppress T cell activation, the T cell receptor signaling pathway and co-stimulatory pathways are crucial targets in RA treatment [66].

The molecular and immunological mechanisms outlined above, including TNF- α , IL-6, JAK/STAT, MAPK, and NF- κ B signaling, directly represent the therapeutic nodes modulated by many phytochemicals. Therefore, the subsequent sections examine how specific classes of plant-derived compounds, such as flavonoids, alkaloids, terpenoids, and phenolic compounds, target these same cytokines and intracellular signaling cascades [67]. By mapping phytochemical action onto these molecular pathways, this review provides a cohesive understanding of how natural products can modulate the immune dysfunction characteristic of RA [68].

Current pharmacological treatments and limitations

Decreasing inflammation, controlling pain, and delaying the disease course are the main goals of current RA treatment approaches [69]. The mainstay RA treatment consists of DMARDs, including methotrexate, the most frequently administered conventional DMARD [70]. Methotrexate can have adverse effects such as fatigue, nausea, and liver damage, although it works well for many patients. Biologic DMARDs that target certain inflammatory pathways have shown potential in situations in which traditional DMARDs are insufficient. These consist of inhibitors of JAK, IL, and TNF [71]. However, because of the formation of anti-drug antibodies, biologic DMARDs can lose their effectiveness over time and are associated with elevated infection risk [72]. Although glucocorticoids, such as prednisone, are frequently used to treat short-term symptoms, they can cause serious long-term adverse effects, such as weight gain, osteoporosis, and elevated risk of cardiovascular disease [73]. Although they decrease pain, NSAIDs might not change the course of a disease and, when used for extended periods, can increase cardiovascular disease risk or cause gastrointestinal problems [74]. A substantial fraction of patients with RA do not experience remission or low disease activity

with current medications, although numerous therapy alternatives are available. Furthermore, many patients' access to biologic DMARDs is restricted by their high cost, particularly in settings with low resources [75, 76]. Because RA is heterogeneous, each patient's response to treatment can substantially differ; therefore, a trial-and-error method is necessary to determine the best course of action. In addition to being time-consuming, this procedure can cause patients to experience needless adverse effects [77]. Concerns regarding possible undiscovered dangers associated with extended use have also been raised, given that the long-term safety profiles of more recent biologic and targeted synthetic DMARDs remain unclear [78]. The burden of managing RA is increased for patients and healthcare systems by the requirement for regular monitoring and laboratory testing to evaluate medication effectiveness and identify any toxicities. Identifying biomarkers to forecast therapy response and individualize treatment plans, as well as creating more targeted medicines with better safety profiles, are becoming increasingly important. Although rheumatoid arthritis treatment has substantially advanced in the past few decades, more accessible, safe, and effective therapeutic choices remain necessary to enhance outcomes for all patients with RA [79].

Herbal remedies in the treatment of rheumatoid arthritis

In preclinical or clinical trials, several medicinal plants have been experimentally confirmed to aid in RA treatment. Pharmacological investigations directly or indirectly assessing the most frequently described medicinal plants used to treat RA are included in this discussion. **Table 1** shows a list of herbal medicines with anti-RA properties.

Bioactive phytochemical classes and their effects

The pathological mechanisms in RA comprise long-term cytokine release (TNF- α and IL-6); NF- κ B and MAPK activation; oxidative stress; and proliferation of FLSs. Against this molecular backdrop, phytochemicals exert their therapeutic effects. Each class of phytochemicals discussed herein acts on one or more of these immunological targets, thereby mirroring or complementing the pharmacological action of biologics and DMARDs.

Flavonoids

Flavonoids, polyphenolic pigments found in a wide variety of fruits, vegetables, and herbs, including tea, ginger, parsley, and onions, have known antioxidant and anti-inflammatory qualities. In RA models, many flavonoids have demonstrated anti-arthritic properties, primarily by inhibiting pro-inflammatory cytokines [80]. One such promising flavonol

is galangin, which is present in propolis, honey, and *Alpinia galanga*. In mice with CIA, galangin has been shown to decrease joint inflammation and suppress the growth of synoviocytes that resemble RA fibroblasts [81]. In synoviocytes, galangin mechanistically decreases TNF- α , IL-1 β , IL-18, COX-2, and inducible nitric oxide synthase (iNOS) levels by downregulating NF- κ B and NLRP3 signaling. This flavonoid prevents oxidative damage to synoviocytes by inhibiting nuclear translocation of NF- κ B and activating antioxidant enzymes, thus increasing SOD while decreasing malondialdehyde [82].

Other flavonoids have shown comparable characteristics. For example, kaempferol, found in tea, broccoli, and apples, has demonstrated anti-inflammatory properties *in vitro*. Kaempferol inhibits the NLRP3 inflammasome cascade (pyroptosis) in RA fibroblasts by binding caspase-1 [83]. By preventing caspase-1 activation, kaempferol treatment decreases RA-FLS migration and proliferation, and markedly decreases the release of IL-1 β and IL-18 [84].

Flavones identical to luteolin and apigenin (found in celery and parsley) have also shown effectiveness in RA models. According to preclinical research, these phytochemicals block synoviocyte inflammatory signaling and lower blood TNF- α and IL-6 in arthritic rats. For example, apigenin inhibits dendritic cell migration and maturation, thus delaying the onset of CIA and decreasing serum TNF- α /IL-1 β ratios [85]. Similarly, by suppressing NF- κ B and modifying Th1/Th17 cytokines (lowering IFN- γ and IL-17), fisetin and hesperidin have been found to decrease arthritis scores in rats. Thus, flavonoids block NF- κ B/MAPK pathways and downregulate pro-inflammatory mediators (TNF- α , IL-6, and IL-17) [86]. Additionally, they enhance antioxidant defenses and anti-inflammatory cytokines (IL-10), which together decrease RA pathogenesis [87]. In agreement with the cytokine-driven inflammation described in Section 3.1, flavonoids inhibit TNF- α and IL-6 signaling by blocking NF- κ B translocation and NLRP3 activation.

Alkaloids

Alkaloids are plant constituents that contain nitrogen and frequently have potent bioactivities. Remarkably, sinomenine, an alkaloid obtained from *Sinomenium acutum*, is used to treat RA in traditional Chinese medicine [88]. According to recent research, sinomenine markedly decreases synovial inflammation. Sinomenine inhibits crucial signaling and decreases MMP9 expression in LPS-stimulated macrophages [89]. MMP9 has been identified as a sinomenine target through network pharmacology analysis and trials. MMP9 is downregulated, and TNF- α /IL-6 production decreases, when activated RAW264.7 cells are treated with sinomenine. According to these results, sinomenine decreases cytokine-driven damage in RA by obstructing the MMP9/NF- κ B axis [90].

Berberine (found in *Coptis* and *Berberis*) is an alkaloid with confirmed immunomodulatory properties. Berberine often decreases IL-1 β , TNF- α , and IL-6 in arthritic animals, partly by changing the gut microbiota and modifying TLR4/

Table 1 Herbal Remedies for Anti-Rheumatoid Arthritis

Scientific Name	Part Used	Active Constituents	Method (Model)	Outcome	References
<i>Aframomum melegueta</i>	Seeds	Essential oils	CFA-induced arthritis in rats	Antioxidant; inhibits NO and COX; decreases paw edema and inflammation	[180, 181]
<i>Ajuga iva</i>	Aerial parts	Flavonoids, Iridoids	CIA rats	↓ IL-1 β , IL-6, TNF- α ; cartilage protection	[182]
<i>Akebia quinata</i>	Stem	Triterpenoids	AIA rats	↓ TNF- α ; anti-inflammatory	[183]
<i>Allium cepa</i>	Bulb	Quercetin	LPS macrophages; AIA rats	↓ NO, PGE2; suppresses NF- κ B and cytokines	[184, 185]
<i>Allium sativum</i>	Bulb	Allicin, ajoene	RAW264.7; rats with CFA-induced arthritis	↓ COX-2, iNOS, TNF- α , IL-1 β , RF	[186]
<i>Aloe barbadensis</i>	Leaf gel	Anthraquinones	LPS RAW264.7; rats with CFA-induced arthritis	↓ COX-2, iNOS, PGE2; ↓ paw swelling	[187, 188]
<i>Alpinia officinarum</i>	Rhizomes	Flavonoids	LPS RAW264.7; rats with CFA-induced arthritis	↓ NO, IL-1 β ; antioxidant	[189]
<i>Ammodaucus leucotrichus</i>	Seeds	Phenolics	CIA and rats with CFA-induced arthritis	↓ MDA, MPO; ↑ GSH; cartilage protection	[190]
<i>Anacyclus pyrethrum</i>	Roots	Alkylamides	Rats with CFA-induced arthritis	↓ Cytokines; antioxidant	[191, 192]
<i>Argania spinosa</i>	Kernel oil	Tocopherols	LPS RAW264.7; mice with CFA-induced arthritis	↓ NO, TNF- α ; macrophage modulation	[193]
<i>Artemisia ivayomogi</i>	Leaves	Flavonoids	LPS macrophages; AIA rats	↓ TNF- α , IL-6; antioxidant	[194]
<i>Asphodelus tenuifolius</i>	Tuber	Phenolics	Rats with CFA-induced arthritis	↓ COX-2, iNOS, TNF- α , IL-1 β , RF	[195, 196]
<i>Bambusa arundinacea</i>	Seeds	Phenolics	RA rats	↓ Paw swelling, TNF- α , RF	[197]
<i>Beta vulgaris</i>	Root	Betalains	AIA rats	↓ TNF- α ; improves antioxidant enzymes	[198]
<i>Boerhavia diffusa</i>	Roots	Punarnavine	LPS cells; LPS mice	↓ TNF- α , IL-1 β , IL-6	[199]
<i>Brassica oleracea</i>	Seeds	Glucosinolates	Rats with CFA-induced arthritis	↓ IL-1 β , PGE2	[200]
<i>Brassica rapa</i>	Roots	Phenolics	LPS macrophages; rats with CFA-induced arthritis	↓ NF- κ B, TNF- α , IL-6, NO; ↑ antioxidant	[201]
<i>Camellia sinensis</i>	Leaves	EGCG	B-cell assay; CIA rodents	↓ BAFF; anti-inflammatory	[202]
<i>Calotropis procera</i>	Latex	Cardiac glycosides	Rats with CFA-induced arthritis	↓ TNF- α , IL-6, PGE2; ↓ joint damage	[203]
<i>Capparis spinosa</i>	Fruit/leaves	Flavonoids	LPS RAW264.7; rats with CFA-induced arthritis	↓ NO, TNF- α ; inhibits COX-2, NF- κ B	[204]
<i>Capsicum annuum</i>	Fruits	Capsaicin	LPS macrophages; rats with CFA-induced arthritis	↓ IL-6, TNF- α ; inhibits COX-2	[205]
<i>Carum carvi</i>	Seeds	Carvone	Rats with CFA-induced arthritis	↓ Swelling, RF, IL-6; antioxidant	[192]
<i>Cassia absus</i>	Whole plant	Anthraquinones	AIA rats	↓ TNF- α , IL-1 β ; ↓ leukocytes	[24]
<i>Caulophyllum robustum</i>	Root	Alkaloids	LPS RAW264.7; CIA mice	↓ IL-1, IL-6, TNF- α ; inhibits NF- κ B	[206]
<i>Ceratonia siliqua</i>	Pods/seeds	Tannins	Rats with CFA-induced arthritis	↓ MDA; ↑ SOD, GSH; joint protection	[26]
<i>Cinnamomum camphora</i>	Leaves	Camphor	LPS RAW264.7; rats with CFA-induced arthritis	↓ TNF- α , NO; ↓ COX-2	[207]
<i>Cinnamomum cassia</i>	Bark	Cinnamaldehyde	LPS macrophages; rats with CFA-induced arthritis	↓ Cytokines; inhibits NF- κ B	[208]
<i>Citrus aurantium</i>	Leaves	Flavonoids	Rats with CFA-induced arthritis	↓ CRP, cytokines; ↓ inflammation	[209]
<i>Citrus limon</i>	Peel/juice	Limonene, flavonoids	LPS macrophages; AIA rats	↓ TNF- α , IL-6; ↑ SOD, GSH	[210]
<i>Coriandrum sativum</i>	Leaves/seeds	Linalool	LPS macrophages; rats with CFA-induced arthritis	↓ Cytokines; antioxidant	[211, 212]
<i>Crocus sativus</i>	Stigma	Crocin, safranal	LPS macrophages; rats with CFA-induced arthritis	↓ NF- κ B, COX-2, TNF- α	[213]
<i>Cucumis sativus</i>	Fruit	Cucurbitacins	RAW264.7; rats with CFA-induced arthritis	↓ IL-1 β , TNF- α ; antioxidant	[214]
<i>Cucurbita maxima</i>	Seeds	Sterols, fatty acids	Rats with CFA-induced arthritis	↓ TNF- α , IL-1 β ; cartilage protection	[215]
<i>Curculigo rhizoma</i>	Rhizomes	Curculigostide A	CIA/AA rats	↓ TNF- α , IL-6; inhibits JAK/STAT, NF- κ B	[216]
<i>Curcuma longa</i>	Rhizomes	Curcumin	LPS macrophages; CIA rats	↓ NF- κ B, COX-2, TNF- α ; antioxidant	[217, 218]
<i>Elettaria cardamomum</i>	Seeds	1,8-Cineole	LPS RAW264.7; rats with CFA-induced arthritis	↓ NO, TNF- α ; ↓ oxidative damage	[219]
<i>Equisetum arvense</i>	Whole plant	Silicic acid	LPS macrophages; rats with CFA-induced arthritis	↓ iNOS, COX-2; antioxidant	[220]
<i>Eucalyptus globulus</i>	Leaves	1,8-Cineole	LPS macrophages; rats with CFA-induced arthritis	↓ IL-1 β , TNF- α ; antioxidant	[221]
<i>Eugenia caryophyllata</i>	Flower buds	Eugenol	LPS RAW264.7	↓ NF- κ B, COX-2, TNF- α	[222]
<i>Ficus carica</i>	Fruit/leaf	Ficrin, polyphenols	Rats with CFA-induced arthritis	↓ Oxidative stress; improved histology	[223]

Table 1 (continued)

Scientific Name	Part Used	Active Constituents	Method (Model)	Outcome	References
<i>Foeniculum vulgare</i>	Seeds	Anethole	LPS macrophages; rats with CFA-induced arthritis	↓ TNF- α , IL-6; antioxidant	[224]
<i>Glycine max</i>	Seeds	Genistein	RAW264.7; CIA mice	↓ TNF- α ; inhibits T-cell activation	[225]
<i>Glycine tabacina</i>	Roots	Isoflavonoids	CIA mice	↓ TNF- α , IL-6; antioxidant	[226]
<i>Glycyrrhiza glabra</i>	Roots	Glycyrrhizin	LPS macrophages; rats with CFA-induced arthritis	↓ TNF- α , IL-1 β ; ↑ antioxidants	[227]
<i>Harpagophytum procumbens</i>	Roots	Harpagoside	Human synovial cells; AIA rats	↓ COX-2, NO, MMPs; ↓ cartilage damage	[228]
<i>Helianthus annuus</i>	Seeds (oil)	Linoleic acid	LPS macrophages; rats with CFA-induced arthritis	↓ IL-1 β , TNF- α ; ↑ antioxidant enzymes	[229]
<i>Illicium verum</i>	Fruit	Anethole	LPS RAW264.7; rats with CFA-induced arthritis	↓ NO, PGE2; ↓ COX-2	[230]
<i>Ipomoea batatas</i>	Tuber	Anthocyanins	RAW264.7; CIA mice	↓ NF- κ B, IL-1 β , TNF- α	[231]
<i>Juglans regia</i>	Leaves	Polyphenols	LPS macrophages; AIA rats	↓ TNF- α , IL-6; ↑ antioxidant activity	[232–235]
<i>Lavandula angustifolia</i>	Flowers	Linalool, linalyl acetate	LPS RAW264.7; rats with CFA-induced arthritis	↓ TNF- α , NO; antioxidant	[236]
<i>Lepidium sativum</i>	Seeds	Flavonoids	Rats with CFA-induced arthritis	↓ Oxidative stress, cytokines	[236]
<i>Linum usitatissimum</i>	Seeds	Lignans, ALA	TNF- α synoviocytes; CIA mice	↓ MMPs; protects cartilage	[237, 238]
<i>Lippia citriodora</i>	Leaves	Verbascoside	LPS RAW264.7; AIA mice	↓ TNF- α , NF- κ B; antioxidant	[54]
<i>Marrubium vulgare</i>	Leaves	Marrubiin	Rats with CFA-induced arthritis	↓ TNF- α ; antioxidant	[239, 240]
<i>Nardostachys jatamansi</i>	Rhizomes	Jatamansone	RAW264.7; rats with CFA-induced arthritis	↓ TNF- α , COX-2; ↓ bone erosion	[241]
<i>Nerium oleander</i>	Leaves	Cardiac glycosides	LPS macrophages; rats with CFA-induced arthritis	↓ NO, TNF- α ; antioxidant	[57]
<i>Nyctanthes arbor-tristis</i>	Leaves, bark	Iridoids	Cell cultures; RA models	↓ inflammatory mediators	[242, 243]
<i>Ocimum basilicum</i>	Leaves	Eugenol, linalool	LPS RAW264.7; mice with CFA-induced arthritis	↓ TNF- α , IL-6; antioxidant	[244]
<i>Olea europaea</i>	Leaves, oil	Oleuropein	LPS macrophages; rats with CFA-induced arthritis	↓ COX-2, iNOS; ↓ TNF- α	[245]
<i>Opuntia monacantha</i>	Pulp/peel	Betalains	LPS RAW264.7; rats with CFA-induced arthritis	↓ IL-6, TNF- α ; antioxidant	[246]
<i>Panax ginseng</i>	Roots	Ginsenosides	RAFLS, T cells; rats with CFA-induced arthritis	↓ NF- κ B, TNF- α ; immunomodulatory	[247, 248]
<i>Peganum harmala</i>	Seeds	β -Carbolines	LPS macrophages; rats with CFA-induced arthritis	↓ TNF- α , IL-1 β ; COX-2 inhibition	[249]
<i>Phoenix dactylifera</i>	Seeds/pulp	Polyphenols	LPS RAW264.7; rats with CFA-induced arthritis	↓ TNF- α , IL-6; inhibits NF- κ B	[250]
<i>Piper longum</i>	Fruit	Piperine	RAW264.7; AIA rats	↓ NF- κ B, IL-1 β , TNF- α ; ↓ COX-2	[251]
<i>Plumbago zeylanica</i>	Roots	Plumbagin	LPS RAW264.7; rats with CFA-induced arthritis	↓ TNF- α , IL-6; inhibits NF- κ B, JAK/STAT	[252]
<i>Punica granatum</i>	Peel/juice	Punicalagin	RAFLS; CIA rats	↓ MMPs, NF- κ B, COX-2	[253]
<i>Ricinus communis</i>	Seeds (oil)	Ricinoleic acid	Rats with CFA-induced arthritis	↓ Inflammatory mediators	[254]
<i>Rosmarinus officinalis</i>	Leaves	Rosmarinic acid	LPS macrophages; rats with CFA-induced arthritis	↓ TNF- α , IL-1 β ; antioxidant	[255]
<i>Sesamum indicum</i>	Seeds, oil	Sesamin	LPS macrophages; CIA rats	↓ TNF- α , IL-6; ↓ COX-2	[256]
<i>Silybum marianum</i>	Whole plant	Silymarin	AIA rats	↓ Leukotrienes; antioxidant	[257]
<i>Tinospora cordifolia</i>	Stem	Alkaloids, terpenoids	LPS RAW264.7; CIA rats	↓ IL-6, TNF- α , NO; ↓ JAK/STAT	[258]
<i>Tripterygium wilfordii</i>	Roots	Triptolide	Macrophages; CIA rats	↓ NF- κ B, MAPK; ↓ cytokines, bone erosion	[259]
<i>Trigonella foenum-graecum</i>	Seeds	Saponins, flavonoids	Rats with CFA-induced arthritis	↓ IL-6, TNF- α ; cartilage protection	[260, 261]
<i>Urtica pilulifera</i>	Leaves	Flavonoids	Rats with CFA-induced arthritis	↓ TNF- α , IL-1 β ; antioxidant	[262]
<i>Withania somnifera</i>	Roots	Withanolides	Rats with CFA-induced arthritis	↓ TNF- α , IL-1 β ; ↑ antioxidant enzymes	[263]
<i>Zingiber officinale</i> Rosc.	Rhizomes	Gingerols, shogaols	RAFLS, CIA rats	↓ NF- κ B, COX-2, TNF- α , IL-1 β	[264]
<i>Ziziphus nummularia</i>	Leaves, stem bark	Polyphenols	LPS RAW264.7; rats with CFA-induced arthritis	↓ NF- κ B, NO, PGE2, TNF- α	[265]

NF-κB signaling; however, few comprehensive mechanistic investigations have been conducted in RA [91, 92]. Piperine, from black pepper, has demonstrated anti-arthritic synergy by inhibiting TNF-α and IL-1β in synoviocytes and increasing the efficacy of corticosteroids [93]. In rats, CIA has been ameliorated by matrine and oxymatrine (found in *Sophora flavescens*), which lower synovial TNF-α and IL-17 levels [94, 95]. In addition, the alkaloid colchicine (found in *Colchicum* spp.) decreases neutrophil-driven inflammation in arthritic models, despite being better known for gout treatment. Alkaloids are attractive immune-targeting drugs, because they often decrease oxidative stress, inhibit NF-κB, and lower inflammatory cytokines and enzymes in RA models [96]. As shown in **Figure 3**, macrophage-derived TNF-α and IL-1β increase synovial inflammation, whereas alkaloids such as sinomenine directly downregulate these pathways, thus linking phytochemical intervention to RA pathophysiology.

Terpenoids

Terpenoids, a structurally diverse class of natural products (also called secondary or specialized metabolites), have shown notable anti-inflammatory and immunomodulatory effects in preclinical models of RA [97]. Evidence from *in vivo* studies, such as those using CIA or AIA models, has indicated that triterpenoids such as boswellic acid and triptolide suppress inflammatory mediators through inhibition of the NF-κB and MAPK signaling pathways [98, 99]. For example, boswellic acid inhibits IKKβ activation

and decreases TNF-α and IL-6 levels in a CIA rat model, whereas triptolide decreases IL-17 and MMP expression in synovial tissues, thus diminishing joint swelling and cartilage damage [99]. Similarly, *in vitro* studies in macrophage or synoviocyte cultures have confirmed that terpenoids such as thymoquinone downregulate COX-2 and iNOS expression, thus corroborating their molecular effects detected in animal models [100]. However, these inhibitory properties are compound-specific rather than widespread across all terpenoids, and direct comparative studies between terpenoid subclasses are limited [101, 102].

Phenolic compounds (non-flavonoid phenolics)

Phenolic acids, curcuminoids, and stilbenes have been explored for their antioxidant and anti-inflammatory properties in RA-relevant preclinical systems; however, the potential mechanistic target of their action should be considered with caution [103]. *In vivo* studies on curcumin and resveratrol have confirmed decreased paw edema and TNF-α and IL-1β expression, as well as restoration of antioxidant enzyme levels via modulation of the NF-κB and Nrf2 pathways [104]. For example, a curcumin treatment in a CIA rat model decreases COX-2 and MMP-9 levels, thus supporting curcumin's disease-modifying potential under experimental conditions [105]. In *in vitro* macrophage and synoviocyte assays, rosmarinic acid and caffeic acid have been revealed to downregulate pro-inflammatory enzymes and cytokines,

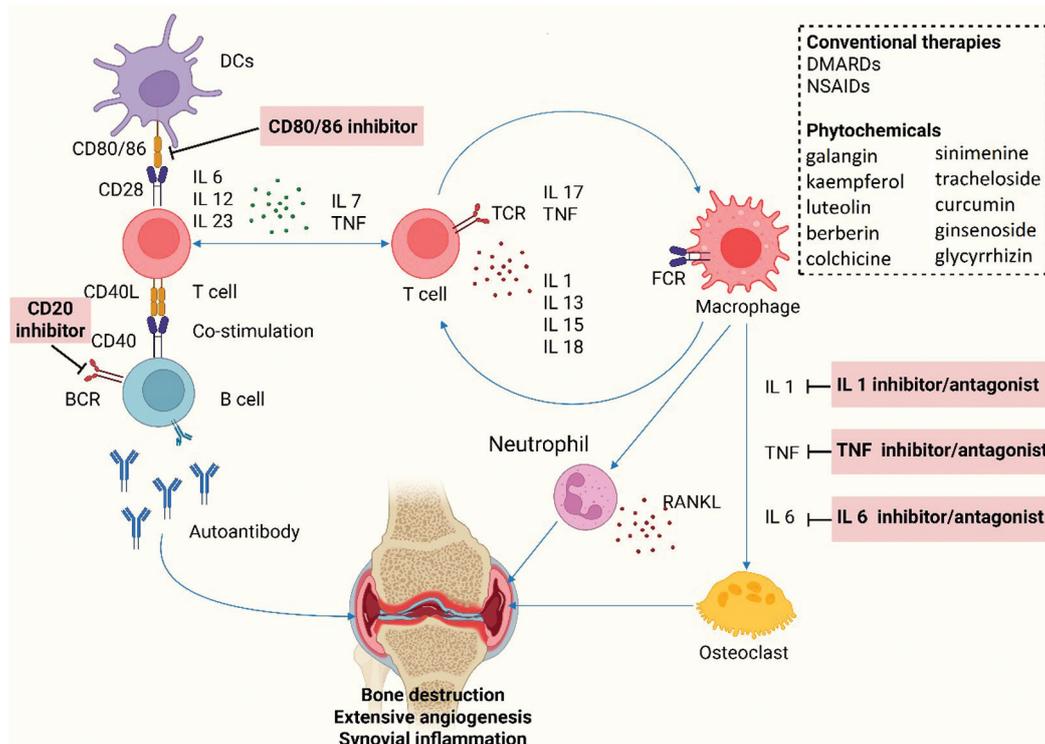


Figure 3 Schematic representation of immune cell interactions and cytokine networks in rheumatoid arthritis pathogenesis, and therapeutic interventions targeting key cytokine pathways (figure created with BioRender.com).

thus providing a molecular justification for their signaling effects [106]. Nonetheless, the pan-class inhibitory report of phenolic compounds on NF- κ B or MAPK signaling should be considered a general trend rather than a universal outcome across all compounds [107]. Many reports have used cell-based anti-inflammatory assays rather than disease-specific *in vivo* RA models, thus limiting the direct traceability of certain mechanistic underlying to RA pathophysiology [108]. Therefore, although evidence supports phenolic compounds as promising modulators of inflammatory cascades, the strength of evidence remains specific to each compound and context, and further standardized studies are warranted to validate comparative efficacy within RA-relevant systems [109].

Saponins

Triterpene or steroidal glycosides, known as saponins, have immunomodulatory properties [110]. Triterpenoid saponins, such as ginsenosides from *Panax ginseng* and *glycyrrhizin* from licorice root, have been investigated in RA models. For example, compound K and ginsenoside Rb1 have been found to decrease splenic Th17 cells and joint swelling in a CIA rat model [111]. Glycyrrhizin decreases TNF- α and IL-1 β by modulating NF- κ B and MAPK [112]. Escin, a saponin derived from horse chestnuts, inhibits the generation of IL-8 and TNF- α in arthritic tissues [113]. Essentially, saponins attenuate cytokine cascades and complement-mediated inflammation by inhibiting pro-inflammatory transcription factors and enzymes. Their amphipathic properties have been found to facilitate phytochemical delivery. Saponin fractions, such as those from *Astragalus*, are widely known to decrease both IL-6 and paw edema in rat arthritic models, despite a paucity of mechanistic evidence [114].

Tannins

Less research has focused solely on tannins (polymeric phenolic compounds, including proanthocyanidins and hydrolyzable tannins); however, plant extracts high in tannins have been shown to be beneficial [115]. Strong antioxidants are found in green tea polyphenols, primarily catechins, a type of flavonoid. *In vitro*, epigallocatechin gallate (EGCG) inhibits COX-2 and TNF- α [116]. In synoviocytes, tannic acid inhibits the nuclear translocation of NF- κ B [117]. In arthritic cartilage explants, ellagannins (such as pomegranate punicalagin) have been found to decrease the synthesis of MMP and IL-6 [118]. Grape seed extract, which is high in proanthocyanidin, has been observed to decrease CIA severity by inhibiting IL-17 [118]. In conclusion, tannins function primarily as antioxidants and moderate anti-inflammatory agents; chelate metal ions; and scavenge ROS, thereby indirectly decreasing inflammatory signals. Additionally, they block matrix-degrading and COX enzymes. Although few *in vivo* studies have focused specifically on RA, tannin-rich extracts have been repeatedly demonstrated to decrease joint damage and cytokine levels [118].

Lignans

Herbs, roots, and seeds all contain lignans, a family of phenylpropanoid dimers [119]. A recent study has demonstrated the anti-RA properties of tracheloside, a lignan derived from *Trachelospermi Caulis*. Tracheloside markedly decreases the release of inflammatory factors and synoviocyte migration *in vitro* [120]. Tracheloside-treated TNF- α -stimulated synoviocytes specifically display decreased expression of MMP-2/3/9, IL-6, IL-17, and COX-2. Additionally, the inactivity of the important signaling proteins JNK and p38 (MAPKs) has suggested that tracheloside inhibits the IL-17/MAPK pathway [121]. Overall, this lignan decreases several pro-arthritic mediators, thereby limiting synovial inflammation. However, data in RA models are lacking. Other lignans such as sesamin and pinoselinol (from plants and sesame) have been shown to alter NF- κ B and arachidonic acid metabolism. However, evidence for tracheloside suggests that lignans target cytokine networks and MAPK in RA pathology [122].

Representative phytochemicals, including their plant origins, experimental paradigms, and documented anti-arthritic activities, are compiled in **Table 2**. In preclinical tests, each class of phytochemicals has generally been found to produce several molecules that lessen joint erosion, inflammatory cytokines, and paw edema.

Synergistic and multi-target actions of phytochemicals in RA management

RA is a multifactorial and network-driven disease, wherein inflammation, oxidative stress, and immune dysregulation occur simultaneously [123]. Consequently, single-target therapies such as TNF- α or IL-6 inhibitors might improve symptoms but frequently fail to achieve durable remission. In contrast, phytochemicals demonstrate synergistic and multi-target pharmacology, by acting on numerous molecular nodes within the same inflammatory cascade [124].

For example, curcumin simultaneously suppresses NF- κ B activation, downregulates COX-2 and TNF- α , and stimulates the Nrf2/HO-1 antioxidant axis, thus achieving dual anti-inflammatory and cytoprotective effects. Resveratrol and quercetin moderate both cytokine expression (TNF- α , IL-6, and IL-17) and intracellular signaling (JAK/STAT and MAPK), while enhancing antioxidant defenses. Similarly, EGCG from green tea decreases B-cell activating factor (BAFF) signaling and inhibits macrophage-derived ROS, thus indicating cross-talk inhibition between adaptive and innate immunity [125].

These combinatorial mechanisms suggest that phytochemicals function not as agents in isolation but as network stabilizers capable of re-balancing immune, oxidative, and metabolic processes. Therefore, phytotherapy is distinct from mono-target methods and aligns with current systems-biology perspectives on chronic inflammatory diseases [126].

Table 2 Anti-rheumatoid Arthritis Phytochemical Compounds from Plant Sources

Phytochemical Class	Phytochemical	Plant Source	Model/System	Key Effects (Mechanism)	References
Flavonoid	Galangin	<i>Alpinia officinarum</i>	LPS-stimulated RA fibroblasts (<i>in vitro</i>)	↓ TNF- α , IL-6, COX-2; inhibits NF- κ B/NLRP3 signaling	[81, 82]
	Kaempferol	Tea, broccoli, apples	RA fibroblasts (<i>in vitro</i>)	↓ IL-1 β , IL-18, caspase-1 activity; inhibits pyroptosis (blocks CASP1)	[83, 84]
	Luteolin	Celery, parsley	CIA model (rat)	↓ IL-17, IFN- γ , ↑ IL-10; suppresses STAT3, NF- κ B signaling (CII model)	[85]
	Apigenin	<i>Petroselinum crispum</i>	CIA model (rat)	↓ Serum TNF- α /IL-1 β ratios	[85]
	Fisetin	<i>Rhus verniciflua</i>	CIA model (rat)	↓ IL-1 β , TNF- α , IL-6/chemokines	[86]
	Hesperidin	<i>Citrus sinensis</i>	CIA model (rat)	↓ TNF- α , IL-6, and IL-17; Block NF- κ B/MAPK	[86]
	Sinomenine	<i>Sinomenium acutum</i>	LPS-stimulated RAW264.7 (<i>in vitro</i>)	↓ MMP9, TNF- α , IL-6; downregulates MMP9/NF- κ B pathways	[88]
	Berberine	<i>Coptis</i> spp., <i>Berberis</i> spp.	CIA model (rat)	↓ IL-1 β , TNF- α ; modulates gut microbiota and TLR4/NF- κ B	[91, 92]
	Piperine	Black pepper	CIA model (rat)	↓ TNF- α , IL-1 β and ↑ effectiveness of corticosteroids	[90]
	Matrine	<i>Sophora flavescens</i>	CIA model (rat)	↓ TNF- α , IL-6, and IL-17; blocks NF- κ B/MAPK	[94]
Terpenoid	Oxymatrine	<i>Sophora flavescens</i>	CIA model (rat)	↓ TNF- α , IL-6, and IL-17; blocks NF- κ B/MAPK	[95]
	Colchicine	<i>Colchicum</i> spp.	CIA model (rat)	↓ TNF- α , IL-6, and IL-17; blocks NF- κ B/MAPK	[96]
	β -Boswellic acid	<i>Boswellia serrata</i>	AIA/CIA model (rat)	↓ TNF- α , IL-1 β ; inhibits COX-2, NF- κ B	[98]
	Triptolide	<i>Tripterygium wilfordii</i>	AIA/CIA model (rat)	Binds TLR4/IL-1R; inhibits NF- κ B/MAPK; ↓ ROS, IL-6, TNF- α , NLRP3	[99]
Phenolic acid and polyphenol	Thymoquinone	<i>Nigella sativa</i> (black cummin)	CIA model (mouse)	↓ IL-17 and MMP expression in synovial tissues	[100]
	Curcumin	<i>Curcuma longa</i>	CIA model (rat)	↓ COX-2, PGE2; inhibits NF- κ B; decreases TNF- α in synovium; ↓ TNF- α , IL-1 β ; inhibits COX-2, NF- κ B; ↑ antioxidants (Nrf2)	[104]
Saponin	Rosmarinic acid	<i>Vitis vinifera</i>	AIA/CIA model (rat)	↓ IL-17/IL-23 inhibits NF- κ B/MAPK	[106]
	Caffeic acid	<i>Coffea arabica</i>	AIA/CIA model (rat)	↓ IL-17/IL-23; inhibits NF- κ B/MAPK	[106]
	Ginsenoside	<i>Panax ginseng</i>	CIA model (rat)	↓ IL-17/IL-23; TNF- α and IL-1 β by modulating NF- κ B and MAPK	[112]
	Glycyrrhizin	<i>Glycyrrhiza glabra</i>	CIA model (rat)	↓ TNF- α and IL-1 β by modulating NF- κ B and MAPK	[113]
Tannin	Astragalus	<i>Astragalus membranaceus</i>	CIA model (rat)	↓ IL-6, MMPs; inhibits NF- κ B/MAPK	[114]
	Punicalagin	Pomegranate peel	Synoviocyte culture	↓ IL-6, COX-2; antioxidant scavenging (anti-NF- κ B)	[115]
Lignan	Catechins	Epigallocatechin gallate	CIA model (rat)	↓ TNF- α , IL-1 β ; antioxidant effect	[117]
	Tracheloside	<i>Trachelospermum caulis</i>	TNF- α -treated MH7A cells	↓ IL-6, IL-17, COX-2, MMP-2/9; inhibits JNK/p38 (MAPK)	[120, 121]
	Sesamin	Sesame seeds	AIA model (rat)	↓ TNF- α , IL-1 β ; antioxidant effect (Nrf2 activation)	[122]
	Pinoresinol	Sesame seeds	AIA model (rat)	↓ TNF- α and arachidonic acid metabolism	[122]

Moreover, evidence from co-administration studies has shown that combining phytochemicals (such as curcumin with resveratrol, or quercetin with EGCG) can achieve additive suppression of NF- κ B and cytokine yield while decreasing the required dose of each compound. Combining these compounds with low-dose DMARDs might increase efficacy and minimize toxicity, thus suggesting a promising path for future translational research [127].

Critical appraisal and limitations of preclinical evidence

Although preclinical studies have provided a strong basis for understanding the anti-arthritic potential of phytochemicals, numerous important limitations warrant careful consideration. A key problem lies in the lack of consistency in experimental design across studies. Differences in animal strains, induction methods (e.g., AIA or CIA), treatment periods, and dosage regimens have hindered direct comparison of results or establishment of dose-response relationships [128]. Many studies have also included small sample sizes or short treatment durations, thus leading to potential overestimation of therapeutic efficacy, and failure to retain long-term toxicity or disease reduction potential [129].

An additional key limitation is the absence of standardization of herbal extracts and formulations. Phytochemical content changes by plant species, geographic origin, harvesting season, and extraction technique, thus leading to notable inconsistencies in pharmacological effects [130]. Limited studies have used chemically characterized or standardized extracts, and many of the active constituents responsible for the observed effects remain unidentified [131, 132].

Moreover, potential publication bias is evident within the current literature. Positive outcomes are commonly reported, whereas studies yielding negative or inconclusive results remain unpublished, thus prompting excessive optimism regarding phytochemical efficacy. The reproducibility of results is further hindered by inadequate methodological transparency, narrow use of appropriate controls, and partial reporting of statistical analyses [133].

Finally, toxicity and safety valuations are often underexplored. Although phytochemicals are generally considered safe, several classes, including alkaloids and terpenoids, might show hepatotoxic or immunosuppressive effects at high doses. Few studies have included comprehensive toxicological evaluations, such as chronic exposure, genotoxicity, or interaction with standard DMARDs [134, 135].

Mechanisms of action

The mechanisms of phytochemical action in RA closely resemble those of the immune and molecular events outlined in the pathophysiology section (Figure 3). By targeting main pro-inflammatory mediators (TNF- α , IL-6, and IL-1 β) and intracellular pathways (NF- κ B, MAPK, and JAK/STAT), these natural compounds interfere at multiple stages of

RA progression from immune activation to joint destruction [136, 137]. NF- κ B signaling is a key pathway. Pro-inflammatory stimuli (TNF- α , IL-1 β , and LPS) in RA cause activation of Toll-like and TNF receptors on immunological and synovial cells, and consequently I κ B kinase (IKK); degradation of I κ B α ; and nuclear translocation of NF- κ B (p65/p50). NF- κ B then stimulates the production of MMPs, COX-2, iNOS, and cytokines (TNF- α and IL-6) [29].

For example, kaempferol and galangin have been found to block synoviocyte NF- κ B activity in the presence of LPS [138]. Sinomenine inhibits NF- κ B signaling by downregulating MMP9, thereby decreasing inflammation [3]. Through preventing TLR4/IL-1 receptor-mediated IKK activation, boswellic acid specifically inhibits NF- κ B [139]. Traditional NF- κ B inhibitors, such as curcumin and resveratrol, alleviate I κ B α and block nuclear translocation of NF- κ B p65. TNF- α , IL-6, IL-1 β , COX-2, and MMP transcription are all decreased by NF- κ B nuclear translocation, which is a commonly observed molecular mechanism in RA pathogenesis of several phytochemicals [111].

MAPKs, which stimulate cytokine gene expression and synoviocyte proliferation, are triggered by pro-inflammatory cytokines [140]. Lignans such as tracheloside directly inhibit JNK and p38 phosphorylation in RA synoviocytes. For example, the terpenoid thymoquinone blocks MAPKs. Phytochemicals decrease the amplification of IL-17, IL-6, and other mediators in RA by inhibiting MAPKs [141].

Another target is the COX-2/prostaglandin E2 (PGE2) pathway. Several phytochemicals suppress the expression or activity of COX-2. For example, when TNF- α is stimulated, synoviocytes treated with trachelosides display decreased COX-2 protein [121]. COX-2 inhibitors include resveratrol and curcumin. These substances diminish joint pain and vascular inflammation by inhibiting COX-2 and PGE2 [3]. However, these mechanisms do not occur in isolation. Most phytochemicals act on multiple intracellular pathways simultaneously, thus synergistically modulating cytokine, oxidative, and apoptotic networks. This polypharmacological nature contrasts with conservative single-target biologics and reflects the intrinsic complexity of herbal matrices [142].

Cytokine modulation, NLRP3 inflammasomes, and pyroptosis

Flavonoids, alkaloids, and other compounds decrease serum/secreted levels of TNF- α , IL-6, IL-1 β , and IL-17 in RA models. For example, sinomenine-treated cells show markedly decreases in IL-6 and TNF- α (via NF- κ B/MMP9 suppression) [1]. Kaempferol-bound caspase-1 decreases the release of IL-1 β and IL-18 by inhibiting pyroptosis [143]. Galangin markedly decreases IL-1 β , TNF- α , IL-18, and IL-6 in synoviocytes [144]. This inhibition prevents the cytokine storm that leads to the development of pannus. Additionally, by upregulating anti-inflammatory cytokines (such as IL-10 and TGF- β), certain phytochemicals alter the Th17/Treg balance. Studies have indicated that flavonoids often increase IL-10 in RA models, thus enhancing inflammation resolution [145], although research in this area is limited.

Oxidative stress and antioxidant effects

Reactive oxygen and nitrogen species, which are found in RA synovium, further deteriorate cartilage. Numerous phytochemicals have strong antioxidant properties [146]. Galangin administration to RA synoviocytes *in vitro* decreases lipid peroxidation marker malondialdehyde (MDA) and increases SOD activity [138]. SOD, catalase, and glutathione peroxidase are antioxidant enzymes that are made in joints after curcumin and resveratrol activate Nrf2. ROS subsequently activate NF-κB, whereas phytochemicals that deactivate ROS prevent oxidative damage and indirectly lower NF-κB activation. Therefore, their anti-cytokine actions are enhanced by their antioxidant activity [3].

Inhibition of matrix metalloproteinases

MMPs, particularly MMP-1, MMP-3, and MMP-9, are overproduced by synovial fibroblasts in RA and break down cartilage collagen. MMP expression is normally suppressed by phytochemicals. Sinomenine decreases MMP9 levels in macrophages [147]. Tracheloside decreases the levels of MMP2/3/9 in synoviocytes activated by TNF-α. Inhibiting MMPs helps maintain joint integrity by preventing the breakdown of cartilage and preserving the structural integrity of the joints. Likewise, diminished PGE2-mediated MMP induction results from a decrease in COX-2. Phytochemicals in arthritis preserve the cartilage matrix by inhibiting these proteases [117].

Apoptosis and cell proliferation

The development of pannus is facilitated by the dysregulated proliferation of FLSs. Some phytochemicals shift the balance toward cell death in hyperplastic synovium or induce apoptosis in FLSs. Flavonoids have been shown to cause apoptosis in FLSs by upregulating p53 and caspase-3 [148]. Triptolide and curcumin have been found to halt the growth of FLSs. Moreover, certain alkaloids cause T cells to undergo apoptosis in immune cells [149].

Mechanistic insights regarding representative phytochemicals in RA

To improve mechanistic understanding, we examined representative compounds from key phytochemical classes to reveal how they modulate RA-relevant molecular targets, such as the NF-κB, MAPK, and JAK/STAT pathways (Figure 4).

Flavonoids such as quercetin and kaempferol exert anti-arthritis effects by suppressing the activation and nuclear translocation of NF-κB p65 in synoviocytes and macrophages [150]. Quercetin inhibits IκBα phosphorylation and stabilizes cytoplasmic NF-κB, thereby decreasing

the transcript levels of pro-inflammatory mediators (TNF-α, IL-1β, COX-2, and iNOS) [151]. Kaempferol further modulates NLRP3 inflammasome and caspase-1 activity, thus decreasing IL-1β and IL-18 release, and controls oxidative stress through Nrf2/HO-1 activation, thus improving SOD and catalase activity. This dual modulation of inflammatory and antioxidant systems is a principal mechanism through which flavonoids restore the redox balance in RA synovium [152].

Among alkaloids, sinomenine and berberine have well-characterized immunomodulatory activity. Sinomenine targets the MMP-9/NF-κB axis in macrophages and FLSs, thereby decreasing the degradation of joint cartilage and increasing protective cytokines [153]. Berberine exerts balancing effects by suppressing JAK2/STAT3 phosphorylation and modulating the gut-immune axis, thus ultimately decreasing Th17 cell differentiation and IL-17 mediated joint inflammation [92].

Terpenoids, primarily boswellic acid and triptolide, strongly inhibit innate immune pathways. Boswellic acid directly inhibits TLR4/IL-1 receptor-mediated signaling, and consequently prevents IKK activation and subsequent NF-κB translocation. This compound also prevents the expression of iNOS and COX-2, thus decreasing PGE2 production and oxidative injury. In contrast, triptolide suppresses JAK/STAT and MAPK signaling in T cells and synoviocytes, and consequently decreases IL-6, IL-17, and MMP-3 expression, while stimulating apoptosis in hyperproliferative synovial fibroblasts [139, 154].

Critical evaluation of preclinical models in rheumatoid arthritis research

Most markers associated with the anti-arthritis potential of phytochemicals have been identified for preclinical investigations using both *in vitro* and *in vivo* models; however, these models substantially vary in their strategies, quality, and translational relevance to human RA. *In vitro* methods such as FLSs (RA-FLSs), RAW 264.7 macrophages, and LPS-stimulated immune cells have provided valuable mechanistic insights into cytokine regulation, oxidative stress, and signaling activation (e.g., NF-κB, MAPK, and JAK/STAT), but they lack the cellular complexity and immune interactions existing in human joints [155]. Among *in vivo* models, the CIA model most closely mimics autoimmune features of human RA, whereas AIA and Complete Freund's adjuvant (CFA)-induced arthritis reflect primarily the inflammatory or degenerative aspects of the disease [156]. Nonetheless, contradictions in experimental design, such as differences in dosage, duration, strain susceptibility, and outcome counting, limit comparability and reproducibility across studies. Furthermore, several models neglect major clinical variables such as sex differences, comorbidities, and chronicity, thus limiting their predictive power for human efficacy [157].

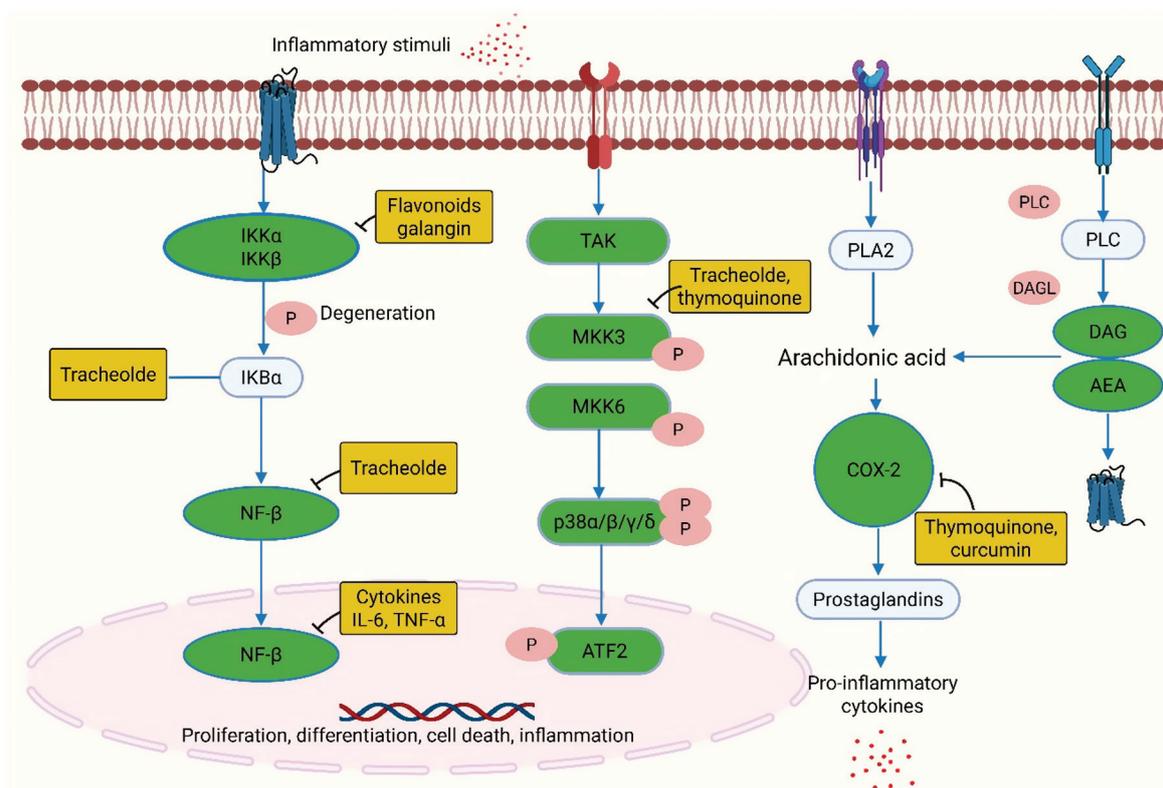


Figure 4 The NF-κB signaling pathway and mitogen-activated protein kinase (MAPK) pathways, including JNK, p38, and ERK $\alpha/\beta/\gamma/\delta$ and cyclooxygenase-2 (COX-2)/prostaglandin E2 (PGE2) pathway, are targets for rheumatoid arthritis (figure created with BioRender.com).

Bridging the translational gap: from preclinical promise to clinical application

Although considerable preclinical evidence supports the anti-inflammatory and immunomodulatory potential of phytochemicals in RA, translation into clinical practice remains limited [3]. Few plant-derived compounds have progressed to clinical evaluation, and current studies have indicated both their promise and persistent challenges. For example, curcumin from *Curcuma longa* has been tested in randomized controlled trials and demonstrated modest improvements in joint pain, swelling, and inflammatory biomarkers when used as an adjunct to methotrexate [217, 218]. In addition, sinomenine, an alkaloid from *Sinomenium acutum*, is clinically used in China for inflammatory disorders, in which it shows DMARD-like efficacy with a satisfactory safety profile [90, 91]. Paeoniflorin, the primary glycoside of *Paeonia lactiflora*, has also entered early-phase clinical trials, which have indicated decreases in TNF- α and IL-6 levels comparable to those achieved by low-dose methotrexate; this treatment therefore has potential as a safer adjunctive therapy (Table 3). However, the lack of large-scale, multi-center trials using standardized formulations limits definitive conclusions regarding clinical efficacy from being drawn [158, 159].

A major barrier to translation is poor bioavailability and pharmacokinetic inconsistency. Numerous phytochemicals, including curcumin, quercetin, and resveratrol, have low

water solubility, rapid metabolism, and partial systemic absorption [160]. Advanced formulation methods, such as nanoparticles, liposomes, phytosomes, and polymeric micelles, have increased stability and tissue targeting in pre-clinical studies but require rigorous human validation. In addition, plant extracts are inherently complex mixtures, and a deficiency in standardization in active compound content complicates regulatory approval and reproducibility [161].

An evolving strategy to improve therapeutic outcomes involves synergistic combinations of phytochemicals with conventional DMARDs or biologics [162]. Limited pre-clinical clinical data suggest that compounds such as curcumin, quercetin, and resveratrol can potentiate the anti-inflammatory effects of methotrexate or TNF- α inhibitors, while mitigating hepatotoxicity and oxidative stress. Such integrative therapeutic regimens have potential to decrease drug resistance, decrease the required doses of synthetic DMARDs, and improve patient tolerability [163].

Key challenges in clinical translation of phytochemicals for RA

Despite promising preclinical outcomes, the clinical advancement of phytochemicals for RA expression faces critical translational barriers that limit their therapeutic use [164]. Major challenges include poor bioavailability and

Table 3 Clinical Trial Landscape of Phytochemicals with High Potential in RA Treatment

Phytochemical/Plant Source	Dose	Trial Phase/Design	Sample Size	Key Outcomes	References
Sinomenine (<i>Sinomenium acutum</i>)	60–180 mg/day oral	Post-marketing clinical application (China)	n>2500 (registry)	Comparable to low-dose DMARDs; ↓ IL-6/TNF- α ; mild GI effects	[90, 91]
Paeoniflorin (<i>Paeonia lactiflora</i>)	120–240 mg/day oral	Phase II; multicenter	n=120	↓ TNF- α /IL-6; improved joint mobility; superior safety vs. MTX	[158, 159]
Resveratrol (<i>Polygonum cuspidatum</i>)	1 g/day oral	Phase I/II exploratory	n=30	↓ Inflammatory cytokines but limited functional improvement	Exploratory
Boswellic acids (<i>Boswellia serrata</i>)	300–500 mg/day oral	Phase II pilot	n=39	↓ Pain and swelling, improved functional scores; well tolerated	Pilot

metabolic instability. Many plant-derived compounds, such as curcumin, quercetin, and resveratrol, exhibit low aqueous solubility, poor intestinal absorption, and rapid metabolic degradation, thus leading to insufficient systemic concentrations. Their limited pharmacokinetic profiles often require high oral doses, which might limit compliance and safety. Approaches such as nanoformulation, liposomal encapsulation, and complexation with phospholipids have shown potential to improve absorption and target tissue distribution, yet these technologies require further optimization and validation in clinical settings [165].

Another major problem is the lack of standardization in herbal extracts. Variability in plant species, geographical origins, harvesting seasons, and extraction methods results in varying phytochemical content and biological potency. This heterogeneity hinders reproducibility across studies and complicates dose-response assessments. The use of standardized excerpts, validated reference markers, and Good Manufacturing Practice compliant processing is important in confirming quality and reproducibility [166].

Toxicological and safety concerns also persist but have not been effectively identified. Although phytochemicals are often perceived as naturally safe, several classes including alkaloids and terpenoids can exhibit hepatotoxicity, nephrotoxicity, or immunosuppressive effects at high doses or with prolonged use [167]. Comprehensive toxicity profiling, including acute, sub-chronic, and genotoxic studies, is therefore essential before clinical translation. Moreover, potential herb-drug interactions, primarily with conventional DMARDs or biologics, must be thoroughly evaluated to avoid adverse pharmacodynamics or pharmacokinetic effects [168].

Regulatory challenges continue to hinder clinical development. Differences in classification frameworks, in which herbal products might be considered dietary supplements, traditional medicines, or pharmaceuticals, create contradictions in consent pathways and quality control requirements. Establishing harmonized international standards and integrating pharmacovigilance systems for herbal formulations would aid in confirmation of both efficacy and safety [167, 169].

Comparison of high-potential phytochemicals in RA therapy

Although numerous phytochemicals exhibit anti-arthritis properties, not all demonstrate equivalent mechanistic robustness or translational promise. To provide a more focused perspective, a subset of high-potential phytochemicals has been prioritized according to three key parameters: (i) mechanistic diversity in modulating multiple signaling cascades relevant to RA (e.g., NF- κ B, MAPK, JAK/STAT, and Nrf2/HO-1); (ii) experimental demonstration of consistent efficacy across in vitro and in vivo models; and (iii) translational relevance according to clinical or pharmacokinetic studies.

Among flavonoids, quercetin and kaempferol are notable for their dual modulation of inflammatory and oxidative

pathways, coupled with reproducible *in vivo* efficacy in collagen- and adjuvant-induced arthritis models [3]. Curcumin, a polyphenolic compound from *Curcuma longa*, the most extensively studied natural agent, exhibits broad inhibition of NF- κ B and JAK/STAT signaling, strong antioxidant activity via Nrf2 activation, and confirmed clinical benefits as an adjunct to methotrexate [217, 218]. Similarly, sinomenine, an isoquinoline alkaloid, has advanced beyond preclinical testing to clinical use in China, and has demonstrated significant immunosuppressive effects and symptom alleviation in patients with RA [90]. Boswellic acid and triptolide, both terpenoids, are supported by rigorous mechanistic data and ongoing clinical evaluation, and therefore are particularly promising for future drug development. Paeoniflorin, a monoterpene glycoside, also exhibits strong translational value: phase II clinical trials have reported decreases in inflammatory cytokines and improved safety compared with synthetic DMARDs [155].

Translational challenges

Although extensive preclinical research supports the anti-inflammatory and antioxidant potential of phytochemicals in RA, their effective translation into clinical application remains limited. Numerous critical challenges hinder the progression of these promising agents from bench to bedside.

Bioavailability and pharmacokinetics

Several phytochemicals have poor oral bioavailability, because of low aqueous solubility, rapid metabolism, and limited absorption across biological membranes [170]. For example, curcumin, resveratrol, and quercetin display effective *in vitro* efficacy but exhibit extremely low plasma concentrations after oral administration [171]. Extensive first-pass metabolism and rapid systemic clearance further decrease their therapeutic potential. Advanced formulation approaches such as nanoparticle encapsulation, liposomes, phytosomes, and polymeric micelles have been used to enhance stability, permeability, and sustained release, but their clinical validation remains preliminary [172].

Metabolic instability and standardization issues

Plant-derived preparations often contain multiple bioactive components whose concentrations can vary according to species, geographical source, extraction method, and storage conditions [173]. This lack of standardization introduces variability in pharmacological outcomes and complicates reproducibility. Moreover, the metabolism of phytochemicals can generate active or inactive metabolites, thereby altering efficacy and safety profiles. Establishing standardized extracts and validated analytical markers is therefore essential for consistent dosing and clinical comparability [174].

Safety and toxicological evaluation

Although phytochemicals are often perceived as safe because of their natural origin, long-term safety data remain scarce. Some compounds, including alkaloids and terpenoids, might exhibit hepatotoxic, nephrotoxic, or immunosuppressive effects at high doses or prolonged exposure. Rigorous toxicological evaluation including acute, subchronic, and chronic studies is necessary to define safety margins and avoid adverse interactions with standard DMARDs [3, 175].

Translational and regulatory barriers

Few phytochemicals used in preclinical RA studies have advanced to well-designed clinical trials. Regulatory frameworks for herbal medicines vary widely among countries, thus posing challenges in defining them as dietary supplements or pharmacological agents. Moreover, robust randomized controlled trials using standardized preparations, adequate sample sizes, and mechanistic biomarkers are lacking. Integrating pharmacokinetic and pharmacodynamic modeling early in the development process could accelerate the translation of promising compounds [176, 177].

Future directions

Bridging existing gaps will require multidisciplinary collaboration among pharmacologists, formulation scientists, and clinicians. Nanocarrier-based delivery systems, synergistic combinations with DMARDs, and systematic toxicological valuations may help overcome bioavailability and safety challenges. Ultimately, well-designed clinical investigations will be crucial to demonstrate preclinical efficacy and validate phytochemicals as reliable adjuncts or alternatives in RA therapy [178, 179].

Conclusion

This review highlights the notable preclinical potential of phytochemicals as modulators of inflammatory and oxidative pathways involved in RA, including their consistent anti-inflammatory, antioxidant, and immunomodulatory effects in targeting key molecular markers such as NF- κ B, MAPK, and JAK/STAT. To translate these promising experimental findings into clinical success, future research should focus on integrating phytochemical discovery using advanced nanocarrier delivery systems to enhance bioavailability and targeted delivery. In addition, exploring combination therapies exploiting synergy between phytochemicals and conventional DMARDs could optimize therapeutic efficacy while potentially avoiding adverse effects. Addressing current limitations, such as heterogeneity in preclinical models, deficiencies in standardized protocols, and inadequate long-term toxicity and pharmacokinetic data, through

well-designed, well-controlled clinical trials will be critical to establishing the true therapeutic value and safety of phytochemicals in RA management.

Abbreviations

RA Rheumatoid arthritis
 DMARDs Disease-modifying antirheumatic drugs
 NSAIDs Nonsteroidal anti-inflammatory drugs
 IL Interleukin
 TNF Tumor necrosis factor
 MMP Matrix metalloproteinase
 NF-κB Nuclear factor kappa B
 MAPK Mitogen-activated protein kinase
 COX-2 Cyclooxygenase-2
 ROS Reactive oxygen species
 SOD Superoxide dismutase
 Nrf2 Nuclear factor erythroid 2-related factor 2
 HO-1 Heme oxygenase-1
 FLSs Fibroblast-like synoviocytes
 CIA Collagen-induced arthritis
 LPS Lipopolysaccharide
 JAK Janus kinase
 STAT Signal transducer and activator of transcription
 NLRP3 NOD-, LRR- and pyrin domain-containing protein 3
 TLR Toll-like receptor
 ACPA Anti-citrullinated protein antibody
 RF Rheumatoid factor

PAD Peptidylarginine deiminase
 MHC Major histocompatibility complex
 DC Dendritic cell
 Th T helper
 Treg Regulatory T
 Tfh T follicular helper
 RANKL Receptor activator of nuclear factor kappa-B ligand
 AIA Adjuvant-induced arthritis
 CFA Complete Freund's adjuvant

Conflict of interest

The authors declare that there are no conflicts of interest.

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